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Arterial Thromboembolic Events following Intravitreal Vascular Endothelial Growth Factor Inhibitor Therapy for Age-Related Macular Degeneration in Regular Clinical Practice

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Arterial Thromboembolic Events following Intravitreal Vascular Endothelial Growth Factor Inhibitor Therapy for Age-Related Macular Degeneration in Regular Clinical Practice

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Epidemiology

By

Oluwatoyin Folasade Fafowora

2015

ABSTRACT OF THE DISSERTATION

An Assessment of Arterial Thromboembolic Events following Intra-vitreal Vascular Endothelial Growth Factor Inhibitor Therapy for Age-Related Macular Degeneration in Regular Clinical Practice

by

Oluwatoyin Folasade Fafowora

Doctor of Public Health in Epidemiology

University of California, Los Angeles, 2015

Professor Anne L. Coleman, Co-Chair

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Intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) is currently the best treatment for neovascular age-related macular degeneration (nvAMD). Anti-VEGF use is associated with concerns about adverse events in the elderly. Some adverse events such as arterial thromboembolic (AT) events, though rare, are potentially fatal. Investigations of AT event risk are typically a secondary objective in clinical trials of anti-VEGF agents. Some studies show increased risk of AT adverse events, while other studies show no appreciable difference in risk.

The MarketScan® insurance claims database provided 90% power to detect differences as low as 5%, and encompassed a nationally representative population, to enable the investigation of rare AT adverse events. I analyzed insurance claims data for 153,019 newly-diagnosed nvAMD patients aged 50 years or older continuously enrolled between 2006-2012. Of the study

participants 41,336 (27.0%) had AT events during the study period, and 76,014 (49.7%) of the study participants received anti-VEGF injections.

I used Cox regression models, with adjustments for selected covariates and propensity score (PS) weighting, to assess the risk factors for AT adverse events associated with anti-VEGF therapy. I also used logistic regression methods to investigate the odds of AT events associated with any anti-VEGF therapy, and used Cox proportional hazards to assess AT event risk for patients in treatment subgroups for each of the three currently used drugs, Bevacizumab (Avastin), Ranibizumab (Lucentis) and Aflibercept (Eylea).

I found a three-fold increase of the risk of new AT adverse events in patients with a history of AT events prior to their nvAMD diagnosis (Hazard ratio [HR] 3.28, 95% confidence interval [CI] 3.21, 3.38). Other covariates associated with higher AT adverse event risk were the medication Plavix (HR 1.59), peripheral arterial disease (HR 1.39), diabetes (HR 1.27), renal disease (HR 1.17), dementia (HR 1.08), Preferred Provider health insurance subscription (HR 1.06), and age (HR 1.17).

The marginal odds ratio I observed for AT events in association with any anti-VEGF therapy was 20% lower (Odds ratio 0.79, 95%CI 0.77, 0.81) than without therapy, in a logistic regression model adjusted for potential confounders. When I included patient time and propensity score weights in the logistic regression, the estimated odds was 1.18 (95% CI 2.2, 1.2), indicating almost 20% marginal increased odds of AT adverse event in association with anti-VEGF, and suggesting that the time element and confounding by indication, are important in consideration of anti-VEGF-associated AT adverse event risk.

Cox regression showed that AT events are up to 20% less likely to occur within the first 30 days, and 10% less likely in days 31-60 after nvAMD diagnosis in patients who received any anti-

VEGF, compared to those who did not. AT events were more likely to occur when follow-up was longer, and my Kaplan-Meier curves portrayed a switch from negative to null risk after 90 days, with no further effect of anti-VEGF after approximately 90 days.

There were no marked differences in AT adverse event risk associated with the individual anti-VEGF medications. Avastin and Lucentis lowered AT event risk in the first 90 days after nvAMD diagnosis by about 10%, and there was no difference in AT risk over the same time period between those who did, or did not receive Eylea.

In conclusion, I identified that a history of AT events prior to the use of anti-VEGF, use of Plavix, peripheral arterial disease, diabetes, renal disease, dementia, Preferred Provider health insurance subscription, and age, were associated with a higher risk of AT events. My observation of change in direction of effect estimates from odds ratio 0.77 to odds ratio 1.18 before and after accounting for patient time on the study, and for confounding by clinical indication (using propensity scores), illustrated the importance of these factors in interpreting any assessment of AT adverse events from insurance claims data. The data in fact indicated a negative risk of AT events associated with anti-VEGF in the first 90 days that switched to a positive risk thereafter - possibly due to increased recognition and preventive treatment for patients on anti-VEGF therapy, compared to patients who were not on treatment.

The dissertation of Oluwatoyin Folasade Fafowora is approved.

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University of California, Los Angeles

2015

DEDICATION

This dissertation is dedicated:

First, to my Father above all fathers, who loves me and gave His Son for me. You make my life well worth living.

To my birth family, Daddy – Dr. M.O.E. Thompson, Olaleye and Tracy, Oladimeji and Taiwo, Jimi and Taiwo, Kehinde, Idowu and Jadesola, I cannot appreciate you enough in one lifetime.

To my “penterascal”, my Truelove, Idowu Olaniran Fafowora. If I had to choose a partner for the race of life over again, you would still be my first and only choice.

To the precious petals that bring continuing love and laughter into my life, Similolu, Fimilolu, Bimilolu, Nimilolu, Kimilolu. You are my joy.

To my mentors Anne Louise Coleman and Michael Bruce Gorin. My seven years at UCLA are gone like a dream – first as your postdoctoral fellow, then as your doctoral student. You are phenomenal coaches.

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BIOGRAPHY

1975-1980	M.B.,B.S. University of Ibadan, Nigeria
1980-1981	Nigerian National Youth Service Year Family Physician, Nigeria Railway Corporation Clinics
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CHAPTER ONE

A Review of Pharmacovigilance Studies for Arterial Thromboembolic Events Associated with Intravitreal Anti-vascular Endothelial Growth Factor Therapy

INTRODUCTION

Age-Related Macular Degeneration (AMD) is an eye disorder resulting from degenerative macular changes that are associated with aging. It is a complex genetic disorder that involves activation of the alternative complement and other biologic pathways that regulate the synthesis and maintenance of cellular lipids and basement membrane substance (Gorin, Genetic insights into age-related macular degeneration: controversies addressing risk, causality, and therapeutics. , 2012). The macula is the central part of the light-sensitive layer in the back of the eye, which enables us to appreciate fine detail. Age-related macular degeneration often begins with the development of yellowish deposits at the level of the pigment epithelium and Bruchs membrane, known as drusen, which accumulate in and around the macula. In time, some eyes show slowly progressive thinning and pigment deposition in the macular tissues that may develop into widespread atrophy (advanced “dry” or atrophic AMD). Alternatively, new blood vessels may grow beneath the retina and leak blood and fluids (“wet” or neovascular AMD [nvAMD]), eventually causing scarring, with permanent damage to retinal cells, in some cases (Zarbin, Casaroli-Marano, & Rosefeld, 2014).

Age-related macular degeneration is the leading cause of blindness among people aged 65 years and older in the developed world (Bressler, et al., 2012). Neovascular AMD accounts for approximately 10% of all AMD cases, but is responsible for 90% of all blindness from the disease, and approximately 200 000 new cases of neovascular AMD are diagnosed in the United States every year (Schachat & D'Amico, 2005).

AMD has now replaced cataract as the most frequent cause of blindness in high-income countries as of 2010. In the United States alone, nearly two million people are estimated to have advanced forms of macular degeneration, and over seven million Americans have earlier forms of the disease with lesser degrees of vision loss, but they carry a life-long risk of progression to advanced disease (Christoforidis, 2011) (Bourne & et al., 2014) (Friedman, 2004).

Importantly, the two factors of longer life spans and aging of the “baby boomer” generation will combine to double the population of Americans aged 65 years or older during the next 25 years to about 72 million. By 2030, older adults will account for roughly 20% of the U.S. population (Centers for Disease Control and Prevention, 2013). The population of nvAMD patients should be expected to increase correspondingly, although interestingly, Klein’s studies in the Beaver Dam offspring cohort revealed lower age-specific prevalence than in the original Beaver Dam cohort (Klein, et al., 2010). Overall, age- and sex- adjusted prevalence (9.1% compared to 16.3%, respectively) and an absence of signs of late AMD, suggested decreasing US incidence of nvAMD. However, the authors noted that a birth cohort effect may have been responsible for their observations.

Treatment options for nvAMD

The current trend of vascular endothelial growth factor (VEGF) inhibition injection therapy for nvAMD is the newest in a progression of nvAMD treatment options ranging from thermal laser photocoagulation in the early 1980’s, through multiple surgical approaches in the 1990’s, to photodynamic therapy in the 2000’s. Pegaptanib (Macugen), an aptamer that binds to VEGF-165, was approved for use by the FDA in December 2004. The therapy slowed down the progression of nvAMD, and in a very small proportion of participants, also improved vision (Gragoudas, Adamis, Cunningham, Feinsod, & Guyer, 2004). Then in 2005, Rosenfeld reported a case-series of nvAMD participants successfully treated with Avastin, an antibody that binds all VEGF-A isoforms (Michels, 2005). Avastin had been FDA-approved for the treatment

of colon cancer, but Michels showed that off-label intravitreal use produced positive results in nvAMD patients, and Avastin has since remained in use for nvAMD treatment. Lucentis, an antibody fragment that binds all VEFG-A isoforms and their biologically active degradation products was FDA approved in June 2006 for the treatment of nvAMD. Lucentis was developed from Avastin by the removal of non-binding segments with the aim of making a small enough molecule to cross the blood-ocular barrier. A newer drug, Aflibercept, was approved by the FDA to treat nvAMD in November 2011. Also known as Eylea, it is a decoy VEGF receptor known as VEGF Trap. Table 1-1 provides important details of these three currently used ocular anti-VEGF therapies.

The cost of anti-VEGF therapy is very high. The combined Medicare 2010 Part B expenditures for Lucentis and Avastin was $2 billion, excluding the substantial cost of office-based imaging, evaluation and management services, and procedures required for delivery of anti-VEGF therapy. The high cost has been shown to be on the increase. Intravitreal injections (CPT code 67028) increased from approximately 1 million in 2009 to 2 million in 2012 in the Medicare population (Levinson, 2012). As the number of patients on anti-VEGF therapy increases, there is mounting concern about the safety of these expensive medications in the vulnerable elderly population in which they are most often used (Lim, L.S., Cheung, Mitchell, & Wong, 2011), and the associated cost of adverse event treatment.

The long-term treatment and high frequency of intravitreal anti-VEGF (anti-VEGF) required in the management of nvAMD may greatly increase individual adverse event risk and costs. For instance, Tseng, et al observed that sustained ocular hypertension occurred more frequently in 23 out of 25 patients with repeated injections of anti-VEGF agents (Tseng, 2012). However Choi, et al observed sustained elevated intra-ocular pressure with injection history in only seven out of 127 patients receiving anti-VEGF, and reported no association with number of injections or injection frequency (Choi, et al., 2011). Kemp also observed no increase in myocardial

infarction (MI) risk with number of injections administered (Kemp, et al., 2013). Albeit, long-term treatment and high frequency of anti-VEGF administration increases the collective number of patients who are at risk of arterial thromboembolic (AT) events while undergoing anti-VEGF treatment, due to the exponential increase in anti-VEGF therapy as first-line treatment for nvAMD and the increasing longevity of the world population (Sivaprasad & Hykin, 2013105).

VEGF functions in many physiological and pathological processes, including maintenance of normal blood vessels, wound healing responses, blood clotting processes, and stabilization of atheromatous plaques (Semeraro, Morescalchi, Parmeggiani, Arcidiacono, & Costagliola, 2011) (Michels, 2005). Treatment is long-term, and participants may need a minimum of a one to two-year course of anti-VEGF every four to eight weeks before seeing benefit or changing course to other therapies (Panel, 2014). Since VEGF plays so many roles in physiologic processes and is used long-term, anti-VEGF therapy is related to several ocular and systemic adverse events.

Table 1–1. Details of the three currently used anti-VEGF drugs

Trade Name	Avastin®	Lucentis®	Eylea®
Generic Name	bevacizumab	ranibizumab	aflibercept
Manufacturer	Genentech	Genentech	Regeneron/Bayer
Indications/Approval	nvAMD off-label	nvAMD June 30, 2006	nvAMD Nov 21, 2011
Molecular differences	149 KDa full-length, bivalent monoclonal antibody against VEGF-A	48 KDa monovalent monoclonal antibody fragment against VEGF-A, minus the Fc domain	115 KDa Fc fusion protein, has binding domains of VEGF receptors 1 and 2 with an Fc antibody fragment

nvAMD=neovascular age-related macular degeneration

Adverse events of ocular anti-VEGF therapy

The Harvard Medical Practice Study defines an adverse event as an event leading to patient harm caused by medical management rather than the underlying condition of the patient that results in measurable disability, prolonged hospitalization or both (Leape, et al., 1991). Drug adverse effects are characterized by two major factors: (i) they have a negative or potentially negative impact on participants; and (ii) they result from some part of the healthcare process, rather than a patient's own actions or disease progression (Walshe, 2000). Ocular adverse events that have been associated with anti-VEGF therapy include intraocular inflammation, intraocular pressure elevation, rhegmatogeneous retinal detachment, infectious endophthalmitis, and ocular hemorrhage (Falavarjani & Nguyen, 2013). Systemic adverse events secondary to intravitreal administration of anti-VEGF therapy include thrombosis, hemorrhage, hypertension, proteinuria, cerebrovascular accidents, myocardial infarction, transient ischemic attacks, deep vein thrombosis, pulmonary embolism, or thrombophlebitis (Semeraro, Morescalchi, Parmeggiani, Arcidiacono, & Costagliola, 2011).

Among the potentially fatal drug adverse events identified with anti-VEGF are (AT) events. AT events are defined as “nonfatal myocardial infarction, nonfatal stroke, and death from a vascular or unknown cause”, on the basis of the classification system of the Antiplatelet Trialists’ Collaboration (Antiplatelet Trialists' Collaboration, 1994).

Older age is a strong risk factor for AT events. The Oxford Vascular Study reported that AT event rates rose steeply with age in their 2002-2005 UK study (The Oxford Vascular Study, 2005) Older age is a strong risk factor for nvAMD as well. Klein’s study of combined data from the Beaver Dam, Rotterdam, and Blue Mountains eye studies showed that people aged 70-79 years were five times more likely, and those aged 80-86 years were 19 times more likely to have nvAMD compared to persons aged 55-69 years (Smith, et al., 2001). If anti-VEGF therapy is associated with increased AT event risk, anti-VEGF therapy can greatly increase the risk of

AT events in nvAMD participants, since their older age already renders them susceptible to AT events.

METHODS FOR IDENTIFYING ADVERSE DRUG EVENTS

There are several different approaches to the investigation of drug adverse event rates, and there are distinct advantages and disadvantages to each approach (Table 1-2).

Table 1–2. Methods for identifying anti-VEGF safety signals

	Description	Advantages	Disadvantages
Post-marketing Regulatory trials	Studies that are conducted to satisfy regulatory requirements for drug safety	Adverse drug events that did not occur during drug development can sometimes be detected	Usually lack statistical power and validity to detect rare adverse events, or increased rates in susceptible populations
Chart reviews	Reviews of physician-recorded clinical observations	Provide detailed patient information and some background to physician decisions; useful for verifying observations made through other methods	Expensive and tedious. Require individual patient consent
Database studies	Studies that use information from databases	Inexpensive, large sample size, do not require individual patient consent because data is de-identified, no clinically-based restrictions in patient selection than seen in regular practice	Not randomized, relevant patient information may be missing or inaccurate, usually no information on subjects that are not included
Pooled estimates and Meta-analyses	Studies that create aggregate estimates from different available sources	Larger sample size than individual studies	Included studies may have varying designs, end-points and patient populations

1. Regulatory studies in ocular anti-VEGF therapy adverse event detection

The occurrence of AT adverse events following anti-VEGF treatment has been investigated in multiple regulatory studies. Regulatory trials are mandated by government health laws and they use randomized controlled trial methods. As randomized controlled trials are very expensive, they are often not powered to detect low-occurrence adverse events such as AT events, and the results cannot be interpreted with great assurance of their validity. Costagliola, et al observed that given the baseline risk of AT events in the nvAMD population, the sample size required to detect a 0.5 relative increase in risk would involve many more participants than are involved in regular clinical trials (Costagliola, et al., 2012). Regulatory studies of anti-VEGF related AT events observed for Lucentis and Avastin are shown in Tables 1-3 and 1-4, respectively. Since off-label use of Avastin does not require regulatory studies, unlike for Lucentis, there are considerably fewer studies that investigate Avastin.

A consideration of the prevalence of AT events observed in regulatory studies that include Avastin and Lucentis showed a variety of designs, varying treatment regimens, many different end-points, and differing patient populations. These differences may be part of the reason no discernible association of AT events and anti-VEGF therapy, and no evidence of an anti-VEGF dose-response was clear. For studies of Avastin, AT event prevalence ranged from 3.2% in untreated participants, to 4.2% in sham-injection treated participants. In studies investigating Lucentis, prevalence rates ranged from 0.0% in participants treated with 0.5 mg Lucentis, to 1.7% in participants treated with 0.3 mg (Tables 1-3 and 1-4). Even when AT events were stratified by type (eg, non-fatal stroke and non-fatal MI), there was no observable association.

Regulatory studies are generally designed for a purpose aligned with the drug development stage in which the study is done and for that reason, they cannot adequately capture adverse event rates (Ray, 2003). Some of the regulatory studies presented in Tables 1-3 and 1-4 were designed primarily to focus on generating information about efficacy (ie, the ability of an

intervention to achieve targeted outcomes under ideal conditions) (Armenian, 2009). Regulatory efficacy studies observe very stringent inclusion and exclusion criteria crafted to fulfill their intended purpose (Hellman & Hellman, 1991) (Victora, Habicht, & Bryce, 2004). For instance, participants with a history or with evidence of severe cardiac disease, or previous MI within six months, or stroke within one year before the study, were excluded from the Macugen phase 3 study (VEGF inhibition study in ocular neovascularization – VISION). Having excluded a good proportion of the population, it is not surprising that no systemic adverse events were reported, and specifically, none involving AT was reported (Chakravarthy, 2006). Studies such as SAILOR and SUSTAIN (Table 1-3) were designed primarily to investigate the side-effects of VEGF inhibitor, Lucentis alone, but a review of the 2008 Medicare nvAMD fee-for-service Part B claims concluded that Avastin actually accounted for 58% of all injections and indicated that it was the standard-of-care treatment for nvAMD in the US; therefore, Avastin should be investigated more often than Lucentis (Brechner, Rosenfeld, Babish, & Caplan, 2011) (Stewart, 2012) (Boyer, Heier, Brown, Francom, Ianchulev, & Rubio, 2009). Additionally, Schmucker, et al observed that studies of Avastin in the literature showed too many methodological limitations to rule out any major safety concerns (Schmucker, et al., 2012).

The “Comparison of Age-Related Macular Degeneration Treatments Trials” (CATT) study was designed to investigate the comparative efficacy of Lucentis and Avastin, and the one- and two-year results of the study were published in 2011 and 2012 (Martin, 2011) (Martin, et al., 2012). The overall conclusion was that Lucentis and Avastin are equally effective for treatment of nvAMD. However, the study was not sufficiently powered to identify meaningful differences in systemic drug-related adverse events and long-term safety, and the patient selection rendered the results not generalizable (Davis, Olsen, Stewart, & Sternberg, 2011). Campbell noted that most of the observed adverse events were conditions not previously associated with inhibition of VEGF, and paradoxically, participants who received fewer doses of Avastin had a greater risk

than those who received more (Campbell, Gill, Bronskill, Paterson, Whitehead, & Bell, 2012). The ANCHOR study (Table 1-3) was a phase 3 trial of Lucentis that did not exclude participants with recent MI or stroke, but investigator discretion allowed exclusion of participants with conditions that might contraindicate the use of anti-VEGF, or place the participant at high risk for complications as an ethical requirement (Brown, 2009). Results from the ANCHOR study showed a higher prevalence of MI for 0.5 mg Lucentis with sham photodynamic therapy (PDT) (3.6%), compared to 1.4% for PDT alone. For stroke, there was no reported event for 0.5 mg Lucentis and sham PDT, but 2.2% for 0.3 mg and sham PDT. The overall rate of MI and stroke in the MARINA study (Table 1-3) were 1.8% and 1.5%, respectively, and they were lower with anti-VEGF use when compared to 2.2% and 4.1% annual rates, respectively, in the general inpatient population (Alexander, Linde-Zwirble, Werther, Depperschmidt, Wilson, & Palanki, 2007) (Rosenfeld, Rich, & Lalwani, Ranibizumab: Phase III clinical trial results., 2006). No clear conclusions can be drawn from these observations.

Table 1–3. Incidence of anti-VEGF related arterial thromboembolic events observed in regulatory studies of Lucentis

Study	Treatment/study type	Participants (nvAMD patients	Treatment regimen/Outcome	Incidence (%)
SECURE (rollover from SUSTAIN) (Silva 2013)	− Lucentis − Open-label, multicenter, phase IV extension study	− n=210	− Lucentis 0.5mg, as needed − 24 months	− AT events: 5.6%
HORIZON (rollover from MARINA and FOCUS and ANCHOR) (Singer 2012)	− Lucentis − Open-label, multicenter, phase IV extension study	− n=600, primary assigned to Lucentis − n=190, crossed to Lucentis from control arm − n=63 , no treatment	− Lucentis 0.5mg as needed − 24 months	− AT events: 5.3% primary assignment and crossover groups; 3.2% in untreated
SUSTAIN (Safety and Efficacy of a Flexible Dosing Regimen of Ranibizumab in NVAMD) (Holz 2011)	− Lucentis − Phase III, multicenter, open-label, single-arm study	− n=513	− Lucentis 0.3mg (0.5mg after Jan 2007), monthly for three months, then as needed for nine months − 12 months	− AT events: 3.7% − MI: 1.0% − Stroke: 10% in treated participants with pre-existing history of cerebrovascular disease
PIER - Phase IIIb sham injection-controlled study of ranibizumab (Abraham 2010)	− Lucentis/sham − Phase IIIb, multicenter, Randomized, double-masked, sham injection-controlled study	− n=182, total − n=59, Lucentis 0.3 mg − n=61, Lucentis 0.5 mg − n=62, PDT	− 0.3 and 0.5 mg monthly for 3 months followed by quarterly injections in association with PDT or PDT alone − 24 months	− AT events: 1.7% for 0.3 mg; 0.0% for 0.5 mg; sham injections not evaluated − MI: (0.0% for 0.3 mg; 0.0% for 0.5 mg; sham injections not evaluated − Stroke: 1.7% for 0.3 mg; (0.0% for 0.5 mg; sham injections not evaluated
ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic CNV in NVAMD) (Brown 2009)	− Lucentis/Visudyne − Randomized, double-masked, sham injection-controlled study	− n=423 total − 0.3 mg with sham PDT n=137; 0.5 mg with sham PDT n=140; PDT with sham injections n=143	− Monthly injections (0.3 or 0.5 mg) in association with sham PDT or with PDT and sham injections − 24 months	− AT events: 4.4% for 0.3 mg with sham PDT; 5.0% for 0.5 mg with sham PDT; 4.2% for PDT with sham injections − MI: 0.7% for 0.3 mg with sham PDT; 3.6% for 0.5 mg with sham PDT; 1.4% for PDT with sham injections − Stroke: 2.2% for 0.3 mg with sham PDT; 0.0% for 0.5 mg with sham PDT; 1.4% for PDT with sham injections

SAILOR (Safety Assessment of Intravitreal Lucentis for NVAMD) (Boyer 2009)	− Lucentis/Lucentis − Randomized single-masked controlled trial	− n=2378 total − 0.3mg n=1169; − 0.5mg n=1209	− 0.3mg or 0.5mg, three monthly loading doses, then as needed − 12 months	− AT events: 2.6% for 0.3 mg; 2.8% for 0.5 mg − MI: 1.2% for 0.3mg; 1.2% for 0.5mg − Stroke: 0.7% for 0.3mg; 1.2% for 0.5mg
FOCUS (RhuFabV2 Ocular Treatment Combined with Visudyne) (Antoszyk 2008)	− Lucentis plus verteporfin/sham plus verteporfin − Randomized single-masked controlled trial	− n=161 total − 0.5 mg n=105 with PDT; PDT alone n=56	− Monthly injections or sham injections − All patients received PDT on day zero and then quarterly as needed − 24 months	− AT events: 4.8% for PDT plus Lucentis; 7.1% for PDT − MI: 0.0% for Lucentis plus PDT; 5.4% for PDT only − Stroke: 4.8% for Lucentis; 0.0% for PDT only
MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody) (Rosenfeld 2009)	− Lucentis/sham − Randomized double-masked controlled trial	− n=716 total − 0.3mg, n=238; 0.5mg, n= 239; and sham n=236	− Monthly injections (0.3 or 0.5 mg) or sham injections − 24 months	− AT events: treated vs sham 4.6% vs 3.8% − MI: 3.4% for 0.3mg Lucentis; 1.3% for 0.5mg Lucentis; 1.7% for sham − Stroke: 1.3% for 0.3mg ; 3.4% for 0.5mg; 1.3% for sham

AT=arterial thromboembolic, MI=myocardial infarction, nvAMD=neovascular age-related macular degeneration, PDT=photodynamic therapy

Table 1–4. Incidence of anti-VEGF related arterial thromboembolic events observed in regulatory studies of Avastin

Study	Treatment/study type	Participants (nvAMD patients)	Treatment regimen/Outcome	Incidence (%)
MANTA (Avastin versus Lucentis in AMD) (Krebs 2013)	− Lucentis/Avastin − Randomized double-masked open-label controlled trial	− n=317	− Avastin n=154 − Lucentis n=163 − Three monthly loading dose, then as needed − 12 months	Avastin − MI: 1.9% − Stroke: 0.6% Lucentis − MI: 1.2% − Stroke: 0.6%
IVAN (Inhibition of VEGF in Age-related Choroidal Neovascularisation) (Chakravarthy 2012)	− Lucentis/Avastin − Randomized double-masked controlled trial	− n=610	− Four groups Lucentis monthly/as needed, Avastin monthly/as needed − 24 months	AT events/hospital admission for heart failure − Avastin: 4% − Lucentis: 6%
CATT (Comparison of Age-Related Macular Degeneration Treatments Trials) (Martin 2012)	− Lucentis/Avastin − Single-masked randomized controlled trial	− n=1208	− Four groups Lucentis monthly/as needed, Avastin monthly/as needed − 24 months	Avastin − Non-fatal stroke: 1.4% − Non-fatal MI: 1.2% Lucentis − Non-fatal stroke: 1.3% − Non-fatal MI: 1.5%
ABC trial (Avastin for Choroidal Neovascular Age-Related Macular Degeneration) (Tufail 2010)	− Avastin/verteporfin, sham − Double-masked randomized controlled trial	− n=126	− Two groups − Avastin three loading injections at 6-week intervals then further treatment if required at 6-week intervals − PDT with Visudyne or sham treatment − 12 months	Avastin − MI: 3.0% Visudyne/sham − 1.5%

AT=arterial thromboembolic, MI=myocardial infarction, nvAMD=neovascular age-related macular degeneration

2. Patient chart reviews in ocular anti-VEGF therapy adverse event detection

The use of information from real-world practice should be more appropriate for the assessment of adverse drug reactions than clinical trials. Manual chart review has been described as the most reliable method for identifying adverse events in real world practice (Naessens, 2009). The retrospective studies and chart reviews listed in Table 1-5 investigated AT adverse drug reactions associated with anti-VEGF therapy using information from patient chart reviews.

There are important differences between the listed studies. The study reported by Carneiro, et al was limited to nvAMD participants while Kemp, et al and Sharma, et al reported adverse events where anti-VEGF was given for any indication (Carneiro, et al., 2011) (Kemp, et al., 2013) (Sharma, John, Johnson, Abouammoh, Hollands, & Brissette, 2012). In addition, the effect measure used for AT events was different in each study, making any comparison difficult. Kemp, et al reported approximately two-fold increased risk for MI, but no increase in risk for stroke while Sharma, et al reported rates, two MIs and one transient ischemic attack (TIA) that occurred within one month after Avastin injection and one TIA within one month following Lucentis injection (table 1-5). Carneiro reported increased odds of AT events with Avastin compared with Lucentis, but the confidence intervals were very wide as a result of the small sample sizes. Carneiro's AT event definition included sudden death and lethal stroke outcomes, but there were no anti-VEGF related deaths in the study.

Clinical information is central to the process of adverse event identification and when detailed clinical history, the diagnostic pathway, and treatment plan are all taken into consideration, a reliable, etiologically plausible conclusion can be reached. When available in digital form, notes from consultations, follow-up visits, admissions, nursing, and discharge notes taken together with clinical test reports from radiology, pathology, and other ancillary departments, provides full information that can be considered the gold standard in adverse event detection. However, patient chart review is expensive and difficult, and while ancillary reports are often available in

digital form, all other reports are usually only available as free-text narratives (Bates, Evans, Murff, Stetson, Pizziferri, & Hripcsak, 2003) (Murff, 2003). With the advent of electronic medical records, adverse event detection by patient chart review may truly become the gold standard, but until then, it is an expensive and cumbersome method for adverse event detection.

Table 1–5. Incidence of anti-VEGF related AT events observed from hospital chart reviews

Study Locations	Indication/Treatment/Data Source	Participants (nvAMD patients)	Assessment Period/Outcome	Incidence (%)
Western Australia (Kemp 2013)	− Any indication − Avastin or Lucentis − Review of hospital and death records 2002-2008	− n=1267, anti-VEGF − n=399, PDT − n=1763, controls −	− 12 months − AT events defined as myocardial infarction and stroke	MI rate − anti-VEGF: 1.9% − PDT: 0.8% − Controls: 0.7% − No difference between anti-VEGF types. Adjusted MI rate 2.3x community or PDF rate − No increase in 12-month MI rate with number of injections − Stroke rate was same for all exposure groups
Ontario, Canada (Sharma 2012)	− Any indication − Avastin or Lucentis − Hospital chart review, 2006-2008	− n=693, Avastin − n=891, Lucentis	− 1 month − AT events defined as: myocardial infarction, ischemic stroke, transient ischemic attack, or pulmonary embolism	AT events − MI: 1.3% for Avastin − MI: 0.3% for Lucentis − Avastin vs Lucentis: OR = 4.26; 95% CI 0.44-41
Portugal (Carneiro 2011)	− nvAMD − Avastin or Lucentis − Hospital chart review, 2006-2010	− n=97, Avastin − n=219 Lucentis	− Less than 3 months and longer than 3 months − AT events defined as: stroke, myocardial infarction, angina pectoris, peripheral thromboembolic disease, transient ischemic, attack, sudden death, and lethal stroke	AT events − Avastin: 12.4% − Lucentis: 1.4% − Avastin vs Lucentis: OR 10.16; 95% CI 2.80-36.93
Four registries: Germany, Netherlands, Belgium and Sweden (Holz 2013)	− Any indication − Lucentis − Hospital chart review − 2011 to 2012	− N=4,444	− 12 months	− MI: 1.1% − Stroke: 4.3%

AT=arterial thromboembolic, CI=confidence interval, OR=odds ratio, nvAMD=neovascular age-related macular degeneration, PDT=photodynamic therapy

3. Clinical database studies in ocular anti-VEGF therapy adverse event detection

Clinical database studies may be the closest ideal for assessing the risk of adverse drug events when the event is rare because databases include large numbers of people. A clinical database study can provide realistic effect estimates because it observes normal clinical practice that is not dictated by any statistically centered protocol attempting to provide comparability between exposed and unexposed groups. Rather, a database can capture a relatively diverse group of patients receiving care in various clinical settings (Stein, Lum, Lee, Rich, & Coleman, 2014). The only inclusion and exclusion criteria are those used in regular clinical practice, thus the study patient population is representative of usual practice, and generalizable to the target population. The large, heterogeneous patient population includes special patient subgroups so that subgroup analyses are meaningful and especially susceptible populations can be identified (Coleman & Greenland, 1995).

The compliance and adherence patterns in a clinical database are representative of real-world patterns, and as a result, estimates of treatment impact are more realistic.. Follow-up for long-term benefits or delayed complications can be accomplished, and there are few ethical constraints. In the investigation of adverse events related to anti-VEGF therapy, off-label use can be investigated in a clinical database without the special funding that mandatory randomized controlled trial studies of adverse events from on-label use requires. Additionally, although administrative claims databases do not include mortality information, they can be linked to mortality records.

International Classification of Disease (ICD) and procedural (CPT and HCPCS) codes are used to operationalize disease definitions in adverse event studies. When they are accurate, these codes are an excellent source of clinically relevant data. However, the codes are included in insurance claims for financial reimbursement and legal documentation, not for research or clinical purposes, and result in variable accuracy for clinical studies. Variable accuracy in a

database may be due in part to hidden incentives to use codes that are biased towards higher paying diagnosis-related groups, or to ensure that participants are classified with diseases in a manner that better ensures insurance reimbursement. Due to differential costs of treatment, there may also be differences between those participants who receive a more expensive anti-VEGF treatment and those who receive the lower cost option. There are significant regional differences in the choice of the therapy as well, and these may also be influenced by the underlying co-morbidities in patients. In addition, there may also be incentives to use certain diagnosis codes in relation to treatment outcome, for instance using one diagnosis code if a patient improves, and selecting another if the patient does not. Although they can be cleverly combined to reflect patient health status and progression of care, codes cannot currently provide important clinical details such as disease severity. Importantly, claims data often do not provide important lifestyle information such as smoking, diet, and exercise (Bates, Evans, Murff, Stetson, Pizziferri, & Hripcsak, 2003). Additionally, disease and procedure classification is progressive. Development of new codes is based on perceived need, and adverse events may not be precisely included in the current coding scheme.

Table 1-6 summarizes three database studies of anti-VEGF-associated AT event risk. Campbell's analyses for ischemic stroke and acute myocardial infarction in a clinical database are shown in more detail in Table 1-7 (Campbell, Gill, Bronskill, Paterson, Whitehead, & Bell, 2012). Campbell's study was conducted in Canada, where access to medical care is not a confounding factor. The patient diagnoses included all manner of retinal diseases as it was not restricted to nvAMD, DME or both as in other studies, and Campbell's study did not detect any increase in risk of ischemic stroke or myocardial infarction associated with anti-VEGF. The number of exposed cases (patients who received anti-VEGF) was small (Table 1-7) and too limited to detect such rare adverse events as AT adverse events. However, two other clinical database studies also did not detect increased risk of ischemic stroke or acute MI with any of

the anti-VEGF therapies (Curtis, Hammill, Schulman, & Cousins, 2010) (Gower, Cassard, & Chu, 2011).

Table 1–6. Hazard ratios of anti-VEGF related arterial thromboembolic events observed from database studies

Study Location	Date/Study type/Data source	Participants	Outcome	Hazard Ratios
United States (Curtis 2010)	− 2005-2007 − Retrospective − Center for Medicare and Medicaid services claim files for participants with fee-for-service coverage	− N=94,686 nvAMD participants aged >65 years − PDT n=52,256 − IV Macugen 36942 − Avastin n=38718 − Lucentis n=19026 − Observed statistically, but not clinically significant differences between treatment groups in demographics and prevalence of comorbidities recorded in the year preceding study index date	− 24 months − Did not analyze for inter-group differences in risk factors associated with AT events	Hazard of mortality − Lucentis vs PDT: HR 0.85 (99% CI 0.75-0.95) − Lucentis vs Macugen: HR 0.84 (99% CI 0.74-0.95) Hazard of MI − Lucentis vs PDT HR 0.73 (99% CI 0.58-0.92) − Avastin vs Lucentis: No difference in HR
United States (Gower 2011)	− Participants initiating treatment in 2008-2009 − Retrospective − Center for Medicare and Medicaid services claim files for participants with fee-for-service coverage	− N=77,886 nvAMD participants aged >65 years − Avastin n=42058 − Lucentis n=35828	− 12 months	Hazard of mortality − Avastin vs Lucentis: HR 1.11 (99% CI 1.01-1.23) Hazard of hemorrhagic stroke − HR Avastin v Lucentis 1.57 (99% CI: 1.04-2.37) Hazard of MI and ischemic stroke − Avastin vs Lucentis: No difference in HR

Canada (Campbell 2012) (Refer to Table 1-7)	− 2006-2011 − Nested case-control study − Ontario, Canada health Insurance plan database	− Participants aged 66 years or older diagnosed as having any retinal disease	− 3706 retinal disease cases and 18530 no retinal disease controls matched on year of birth, sex, history of AT event outcome in last five years, and for diagnosis of diabetes − Did not analyze for inter-group differences in risk factors associated with AT events	− Stroke: OR for exposure to Avastin was 0.95 − MI: OR for exposure to Avastin was 1.04 − Stroke OR (adjusted) for exposure to Avastin was 0.87 − MI: OR for exposure to Avastin was 0.90

AT=arterial thromboembolic, CI=confidence interval, HR=hazard ratio, MI=myocardial infarction, nvAMD=neovascular age-related macular degeneration, OR=odds ratio

Table 1–7. Campbell's analyses for anti-VEGF related ischemic stroke and acute myocardial infarction

Exposure	Cases	Controls	Total
Ischemic Stroke			
Exposed			
Ranibizumab	94	555	649
Avastin	44	238	282
Unexposed	1339	6556	7895
Total	1447	7349	8826
Acute Myocardial Infarction			
Exposed			
Ranibizumab	141	797	938
Avastin	73	364	437
Unexposed	715	9849	10564
Total	929	11010	11939

Unadjusted odds ratio $_{Lucentis}$ 0.83 (0.66, 1.04)
Adjusted odds ratio$_{Lucentis}$ 0.87 (0.68, 1.10)
Unadjusted odds ratio$_{Avastin}$ 0.91 (0.65, 1.26)
Adjusted odds ratio $_{Avastin}$ 0.95 (0.68, 1.34

Unadjusted odds ratio$_{Lucentis}$ 0.86 (0.71, 1.04)
Adjusted odds ratio$_{Lucentis}$ 0.90 (0.72, 1.11)
Unadjusted odds ratio $_{Avastin}$ 0.98 (0.75, 1.27)
Adjusted odds ratio $_{Avastin}$ 1.04 (0.77, 1.39)

UNADJUSTED - Matched on age, sex, history of outcome, and diabetes.
ADJUSTED - Matched on age, sex, history of outcome, and diabetes; adjusted for: ischemic stroke—angiotensin converting enzyme (ACE) inhibitors, acetylsalicylic acid/dipyridamole, cancer in previous 5 years, clopidogrel, hypertension, chronic renal insufficiency, warfarin; acute myocardial infarction—digoxin, ACE inhibitors, cancer in previous 5 years, clopidogrel, diuretics (regular), hypertension, No of unique prescriptions, chronic renal insufficiency, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, warfarin; venous thromboembolism—digoxin, glaucoma therapies, ACE inhibitors, cancer in previous 5 years, diuretics (potassium sparing), diuretics (regular), low molecular weight heparin, No of unique prescriptions, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, warfarin; congestive heart failure—digoxin, glaucoma therapies, ACE inhibitors, calcium channel blockers, cancer in previous 5 years, clopidogrel, diuretics (potassium sparing), diuretics (regular), hypertension, chronic renal insufficiency, warfarin

4. Systematic reviews and meta-analyses in ocular anti-VEGF therapy adverse event detection

Systematic reviews, pooled estimates and meta-analyses are very useful tools for aggregating the wealth of information from different studies of the association between AT events and anti-VEGF use. The goal of these tools is to employ all available data in providing an unbiased estimate. However, a number of the reviews of scientific literature on anti-VEGF therapy are suggestive of conflicts of interest (Bressler, et al., 2012) (Rosenfeld, Rich, & Lalwani, 2006) (Schmidt-Erfurth, 2010) (Schmucker, et al., 2012) (Singh & Kaiser, 2007).

Ueta's meta-analysis of eleven randomized controlled trials (RCTs) of systemic vascular safety of Lucentis in nvAMD showed an increase of cerebrovascular accidents (stroke) with the regimens of 0.5 mg dose versus no drug or sham treatment (OR, 2.27; 95% CI, 0.90-5.69; P = 0.08), 0.5 mg dose versus 0.3 mg dose (OR, 1.79; 95% CI, 0.79-4.06; P = 0.10), and with monthly treatment compared with as-needed (PRN) treatment (OR, 2.04; 95% CI,0.94-4.45; P = 0.07) (Ueta, Mori, Kunimatsu, Yamaguchi, Tamaki, & Yanagi, 2011). The meta-analysis also inferred increased risk of ischemic stroke with Lucentis, but the increase was not statistically significant. Thulliez, et al performed a systematic review and meta-analysis of 21 parallel, randomized clinical trials comparing intravitreal Lucentis or Avastin with no treatment (sham) or with non-antiangiogenic treatment for nvAMD, diabetic macular edema and retinal vein occlusion (Thulliez, et al., 2014). They concluded that ocular anti-VEGF therapy increased the risk for stroke appreciably, but not statistically significantly (OR, 1.61; 95% CI 0.85-3.05), and it did not statistically significantly increase the risk for MI (OR, 0.92; 95% CI 0.54-1.59), in comparison with control treatments such as sham injections or laser, and verteporfin with photodynamic therapy (PDT). Solomon et al performed a Cochrane review of 12 RCTs comprising 5496 participants that compared Macugen, Lucentis, or Avastin against each other, or a control treatment (sham treatment or photodynamic therapy) (Solomon, Lindsley, Vedula,

Kryzstolik, & Hawkins, 2014). They concluded that the occurrence of serious systemic adverse events was comparable across anti-VEGF-treated groups and control groups, but noted that the numbers of events and trial participants may have been insufficient to detect a meaningful difference between groups. Another Cochran review of nine RCTs, of the systemic safety of Avastin versus Lucentis found a prevalence rate ratio of 0.92 (95% CI 0.62, 1.37), indicating 18% lower AT adverse event risk with Avastin than with Lucentis (Moja, et al., 2014). The disease-specific values for MI and stroke rate ratios were very similar (0.84, and 0.83 respectively).

Overall, results from the clinical trials, chart review studies, clinical databases, and meta-analysis generally indicate no defined association of AT events with anti-VEGF intravitreal therapy. The studies are not powered enough to correctly assess the risks or identify susceptible subgroups and they often utilize varying definitions for AT events, causing difficulty in comparing them appropriately.

I propose to assess AT events associated with the use of VEGF inhibitors in the treatment of nvAMD in a real-world clinical database study that is sufficiently powered to detect low-rate adverse events, as well as identify susceptible populations by investigating interactions with comorbidities or concomitant medications.

CHAPTER TWO

The Source Data

SAMPLE SIZE

All three studies reported in this manuscript are based on a sample of 153,019 nvAMD participants who were continuously enrolled in the MarketScan® Commercial Database between January 1, 2006 and December 31, 2012. Of the nvAMD participants included in the studies, 41,336 had a record of MI or stroke following their diagnosis of nvAMD, of which 20,751 (50.2%) received anti-VEGF. A total of 111,683 participants had no record of MI or stroke following their diagnosis of nvAMD and 61,812 (54.7%) of these participants received ocular anti-VEGF therapy.

DESCRIPTION OF THE MARKETSCAN® DATABASE

The MarketScan® Commercial Database contains health claims records created for the purpose of reimbursement for individuals covered by employer-sponsored health insurance and their dependents in the United States (MarketScan, 2012). The MarketScan® Medicare Supplemental Database focuses on patients ages 65 years and older with standard Medicare coverage plus employer-paid commercial plans. The databases span both employer-paid and Medicare-paid components of healthcare. They contain inpatient admission records, outpatient services, prescription drugs, eligibility status, and costs of services. Both databases are fully compliant with the Health Portability and Accountability Act of 1996 (HIPAA), and all data included are de-identified to protect the privacy of patients and providers. Together, these databases represent the health services of approximately 138 million employees, dependents, and retirees in the United States across the period of this study. All enrollment records and inpatient, outpatient, ancillary, and drug claims are included in the database. The person-level information captures clinical utilization, expenditures, and enrollment across inpatient, outpatient, prescription drug, and clinical services from insured employees under 65, and their dependents. The database

includes fee-for-service and fully/partially capitated plans. It contains eight tables: inpatient admission, facility header, inpatient services, outpatient services, aggregated population, outpatient pharmaceutical claims, annual enrollment, and enrollment detail table.

The large size of the MarketScan® nvAMD cohort enabled provision of robust effect estimates for the rare occurrence of AT events related to ocular anti-VEGF therapy. Subgroup analysis was meaningful since the subgroups were large, and a susceptibility profile could therefore be developed for the association under study. Additionally, the comparison of currently available anti-VEGF therapies was valuable as it compared the drugs in a real-world setting rather than a regulatory setting in which they have often been compared. My source population was uniform, as they were all nvAMD participants, while many comparable studies include participants on treatment for diabetic macular edema and retinal vein occlusion. My results can be compared with similar investigations in the Medicare population since my study population is demographically similar to, and includes the Medicare population. However, my results are more generalizable since the population includes participants from age 50 years upwards while the Medicare nvAMD population is aged 65 years and above.

My medication information can be regarded as valid because it was not only about medications prescribed, but those dispensed at a cost. This is important since patients are unlikely to pay out for medications that they will not use.

Participants in my study were enrolled on first record of nvAMD diagnosis. To avoid survival bias, they were newly diagnosed, and therefore could not have been exposed to anti-VEGF therapy prior to their enrollment. Data for AT events that were recorded in the 365 days before nvAMD diagnosis was obtained for analytic purposes, and only AT adverse events recorded after the nvAMD diagnosis date were considered to be related to anti-VEGF therapy. Another possible bias could have been differential loss to follow-up. Clearly, selective loss to follow-up

could limit interpretation of results from a cohort study using an existing database, but Rothman described an insurance claims database (such as the MarketScan database) as a thorough system of surveillance for a follow-up study and my cohort was a closed one (Coleman & Greenland, 1995) (Rothman, Greenland, & Lash, 2008).

Studies that have used MarketScan® research database

Hatoum, et al used MarketScan® Research Data to study the pattern of hypomethylating agents (HPA) used in the treatment of myelodysplastic syndromes (MDS) (Hatoum, 2011). They observed that the median number of days per treatment cycle was the same for the two drugs they investigated though their labeling recommended different numbers of days. Their study indicated that the MarketScan® dataset reflects the real-world use of a drug rather than the recommendations included in a label. The authors were able to discern that less than 5% of patients with MDS receive treatment with HPAs, but the database did not provide clinical information for determination of disease severity, thus it was not clear if severity of MDS correlated with HPA treatment.

Babu, et al observed that four previous studies with sample sizes of 24, 29, 289, and 93 had compared paddle lead and percutaneous lead implantation with respect to outcomes such as clinical symptoms and migration rates; however, results varied, partly due to the small sample sizes (Babu, et al., 2013). Using MarketScan® Research Data, they compared the two procedures with respect to complications, reoperation rates, and long term health-care costs, in a large cohort (9072 persons resulting in 4536 matched pairs) to provide robust effect measures. However, they observed that the database did not provide clinical information such as radiological information for assessment of migration rates or the reason for the reoperations that were included in assessment of the reoperation rate. In addition, the use of CPT codes did not always provide an accurate representation of a patient's procedure or the type of lead used.

In an investigation of the clinical consequences of venous thromboembolism prophylaxis in medically ill patients, Baser, et al examined data from 4467 patients from the MarketScan® Research Database (Baser, et al., 2013). The study had the advantage over previous studies, since the use of anticoagulants and mechanical compression during hospitalization could be captured, as the MarketScan® Database combines hospital and claims data. However, they observed that the low event rates in their sample size were too small for subgroup analysis.

The MarketScan® Research and Optum Databases were the source for a cohort study comparing the risks of opioid abuse by Cepeda, et al (Cepeda, 2013). They observed that ICD-9 codes for abuse and dependence were not clearly delineated, and opioid abuse was likely underestimated in these claims databases. The underestimation could have been due to lack of recognition of the condition, reluctance to put a potentially damaging diagnosis in a patient's record, especially in the absence of certainty, or reimbursement considerations that could affect which diagnosis codes to use. Cepeda, et al noted that the incidence of opioid abuse was more than ten times lower in their claims database studies when compared to regular prospective studies, possibly as a result of underestimation, as well as the existence of multiple sources of illicit use of prescription drugs that could not be captured in the database.

Johnston, et al studied the association between outpatient hypoglycemic events and fall-related fractures in over 300,000 US patients aged 65 years or older with type 2 diabetes (Johnston, 2012). Earlier studies with the same goal examined the association between insulin use and fractures; however, Johnston's study directly measured the association between fall-related fractures and the hypothesized mechanism of increased fracture risk that can result from hypoglycemic medications. The authors observed that the MarketScan® Database's lack of clinical details such as plasma glucose levels, severity of diabetes, and bone mineral density did not allow disease severity to be known within the ICD-9 coding frame that was used for

analysis. For instance, the only indicator for hypoglycemia was that the condition was severe enough to warrant medical attention.

In a propensity matched study of bone morphogenic protein use during spinal fusion surgery and cancer risk, Lad, et al analyzed a matched set totaling 2688 patients from the MarketScan® Database with four years follow-up after a lumbar fusion (Lad, 2013). Lad, et al concluded there was no statistically significant association; however, a larger sample size and longer follow-up were required for further evaluation.

A total of 23,941 women from the MarketScan® Research Database were included in a study by Okoroh, et al that investigated the prevalence of venous thromboembolism and polycystic ovary syndrome as a risk factor for venous thromboembolism (Okoroh, 2012). They observed that a substantial proportion of patients with venous thromboembolism managed in outpatient settings were not generally included in hospital-based studies. The MarketScan® database not only included patients from both inpatient and outpatient settings, it was also geographically diverse, resulting in a robust prevalence estimate. Since the number of patients in the database was large, subgroup analysis was feasible. It resulted in the identification of a specific phenotype as having the highest prevalence of venous thromboembolism. However, since clinical data were not available, it was not possible to determine the reasons for increased prevalence in the subgroup identified. Okoroh, et al reported that it was difficult to operationalize the clinical definition of metabolic syndrome within the claims database, and that they did not have information to report on the racial makeup of the study population.

Limitations of MarketScan® database studies

The preceding review of Marketscan® database studies show that are certain challenges that must be anticipated with use of an insurance claims databases such as the MarketScan®

database for adverse drug event assessment, and I observed some of the challenges in the conduct of my study (Huang & Davis, 2013) (Stein, Lum, Lee, Rich, & Coleman, 2014).

MarketScan® data was collected for reimbursement purposes, and did not provide clinical details by which diagnoses of myocardial infarction, stroke could be verified. Patients who were wrongly diagnosed may have been included in my study. Such wrongful diagnosis would affect both anti-VEGF-treated and untreated patients, and constitute a non-differential misclassification bias, that would alter my estimate of AT event risk away from the null if there was over-diagnosis, and toward the null if there was under-diagnosis of the outcome. Further, myocardial infarction and stroke are diseases that may go undiagnosed without special medical attention. Patients who received anti-VEGF had regular hospital visits for their injections, and may have been diagnosed more frequently with MI and stroke than patients who were not receiving anti-VEGF. Differential misclassification bias could result in my overestimating the association of arterial thromboembolic events with anti-VEGF therapy.

MarketScan® data is claims data information, it was not designed for the purpose of assessing patient exposure to anti-VEGF. While the need for reimbursement probably ensured that records of every anti-VEGF injection was available, and recall bias was therefore not an issue, any anti-VEGF given by providers outside the documented insurance network for a patient would not be recorded. Information bias due to lack of outside-network records of anti-VEGF would attenuate my AT adverse event estimates toward the null. However, the deliberately sequential nature, and the expense of AMD treatment, makes it likely that any patient was treated by one in-network provider at a time.

Laterality of the injected eye was not indicated in the database, but this was not considered a drawback since I was concerned only with the systemic effects of anti-VEGF.

ICD-9 codes and procedure codes were used to document patient diagnoses, clinic visits, treatment procedures, and medications dispensed to patients in the MarketScan® database (Appendix I). Patient diagnoses of comorbidities, number of clinic visits, number of medications dispensed to patients, and other covariates were considered confounders in my investigation of AT adverse event risk. Misclassification of confounding covariates as a result of miscoding could lead to residual confounding and apparent effect measure modification in my assessments. Miscoding could be accidental, or deliberate for reasons of financial incentive. Accidental miscoding would be random, giving rise to random measurement error, but deliberate miscoding would bias my AT adverse events estimate. Suppose for instance, the record of diagnosis of nvAMD was not the same for patients receiving Avastin compared to Lucentis, because insurance reimburses for the use of Avastin, but not Lucentis in nvAMD patients. With deliberate miscoding, the recorded number of nvAMD patients exposed to Lucentis would be reduced, and the resulting differential misclassification would bias my drug-specific comparison of AT adverse event risks away from the null.

Certain covariates that are known to affect the association of AT adverse events with anti-VEGF were not measured for the MarketScan® database. Physician information, records of nvAMD severity and other clinical parameters that determine anti-VEGF-treatment preferences are missing. Lifestyle information about smoking, diet, and other factors known to influence AT event risk was not available. There was no information about socio-economic status in the database, even though there may be differences between those patients who receive a more expensive treatment such as Lucentis, and those who receive the lower cost option such as Avastin. Smoking, in particular, has long been recognized as a cause of adverse health effects, but the confounding occasioned by the lack of these data is non-differential, and should lead to a bias of my estimate of AT adverse events towards the null (Ritz, et al., 2007).

Information in the Marketscan® database does not include information for Americans who are uninsured. It is possible that persons who have nvAMD, MI or stroke make greater effort to enroll in insurance plans than persons who do not. The direction of the selection bias due to lack of insurance could be an over- or an under-estimation depending on which covariates drive the decision to be insured or not insured. Further, practice patterns differ, and the differences could give rise to a selection bias. For instance Dr Gorin observed that nvAMD patients seen at large academic medical centers are routinely placed on anti-VEGF (personal communication, 2015). Patients in the MarketScan® database are treated by such a variety of physicians with a range of treatment capabilities that only 50% of nvAMD patients were treated with anti-VEGF.

There are a few other limitations in using the database for my study. Provider information was not available, even though there may have been medication usage patterns that were related to provider information. There was no mortality data in Marketscan®, although the standard definition of AT events includes vascular death. I limited my outcome definition to MI and stroke, and including only participants who were enrolled 2006-2012 may have biased my effect assessment towards null since the most extreme outcome was not included.

POWER CALCULATIONS

Assuming a total sample size of 100,000, a conservative estimate in the data being used, power was calculated for a variety of effect sizes. These studies have high power to detect effects, even if AT events only occur in 5% of the sample and the differences between those exposed and not exposed to anti-VEGF treatment is as small as 10% (OR, 1.1), the current sample will provide power of .907 to detect clinically significant odds ratios (Figure 2-1). For an OR of 1.1 and response probability of .05, power was .907 and for an OR of 1.1 and response probability of .10, power was .995. For all other conditions examined, power was > .999 (Table 2-1).

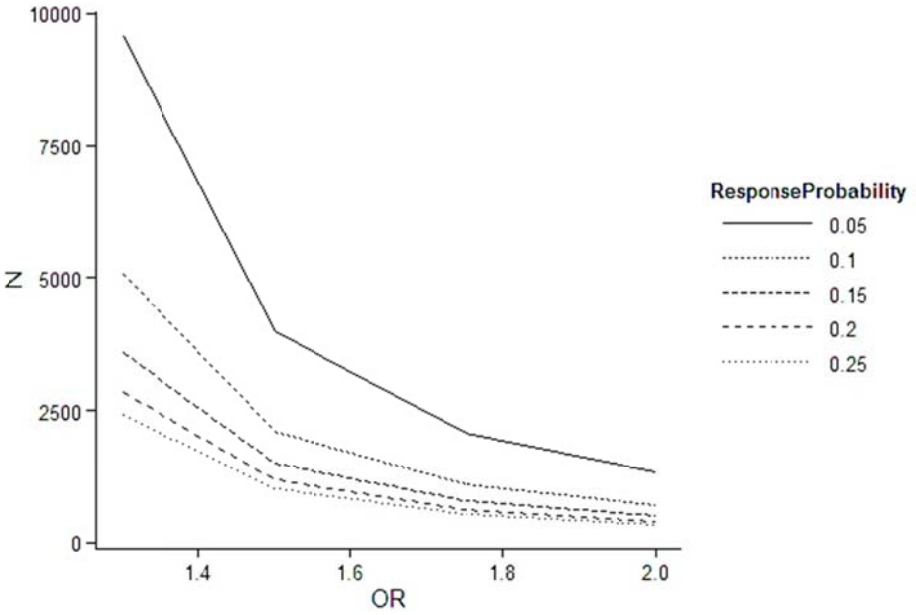

Figure 2–1. Sample size required for power of .80 for differing outcome (AT event) probabilities and odds ratios

OR – odds ratio

N – sample size

Table 2 -1. Estimated power given N=100,000 fixed sample size

Response Probability	Odds Ratio	Power
0.05	1.1	0.907
0.05	1.3	>.999
0.05	1.5	>.999
0.1	1.1	0.995
0.1	1.3	>.999
0.1	1.5	>.999
0.15	1.1	>.999
0.15	1.3	>.999
0.15	1.5	>.999
0.2	1.1	>.999
0.2	1.3	>.999
0.2	1.5	>.999
0.25	1.1	>.999
0.25	1.3	>.999
0.25	1.5	>.999

PATIENT SELECTION

Eligibility

To be eligible for any of my three studies, persons had to be aged 50 years or older and continuously enrolled in their health plan for the twelve months of each selected year within the period between January 1, 2006 and December 31, 2012. They had to have a diagnosis of nvAMD (ICD-9 code 362.52) on at least two separate claims in that year to ensure that the diagnosis of nvAMD was not a tentative, but an established diagnosis. Eligible participants had

to be enrolled for at least 365 days prior to the first nvAMD diagnosis to ensure adequate record of the participants' health status and medication history prior to nvAMD diagnosis. The study period was selected to cover periods when anti-VEGF therapy was becoming a treatment of choice for nvAMD.

Index date

The index date for all participants was their first recorded nvAMD diagnosis date.

Study period

I defined the study period as the time between the first record of nvAMD diagnosis (index date) and the date of AT event thereafter (censor date). In cases where there was no AT event, last service date (exit date) before December 31, 2012 was considered the end of the study period.

Inclusion criteria

- Aged 50 years or older in the year they were selected for the study
- Diagnosis of nvAMD
- Enrolled in the 365 days prior to index date

Exclusion criteria

- Less than 50 years of age at time of diagnosis; these patients were not considered to have nvAMD since by definition the disease rarely occurs in persons below age 50 years
- Less than two recorded diagnoses of nvAMD; patients with only one recorded diagnosis were considered as nvAMD suspects only
- Not enrolled in their health plan for 365 days prior to their first nvAMD diagnosis; these patients did not have adequate information about their pre-nvAMD diagnosis health status

- A record of anti-VEGF injection occurring before nvAMD diagnosis; these patients were not considered to be newly-diagnosed nvAMD cases (only newly-diagnosed cases were included in order to avoid a survivor bias)

Outcome of interest

The outcome of interest was AT events. The Antiplatelet Trialists' Collaboration defined AT events as nonfatal MI, nonfatal stroke, and death from a vascular or unknown cause. Since mortality data are not available in the MarketScan® Research Database, only inpatient or outpatient diagnoses coded were considered as outcomes of interest for my studies. These included nonfatal myocardial infarction (ICD-9, 410, 411.0) and nonfatal stroke (ICD-9, 430-437.2, 438).

Exposure (intervention)

Participants who were considered exposed to anti-VEGF therapy were those who had CPT Code for intravitreal injection (67028). These included Avastin (HCPS code J9035 [injection, Avastin, 10 mg]), Lucentis (HCPS code J2778 [injection, Lucentis, 0.1 mg]), Eylea (HCPCS code C9291, Q2046, or J0178 [Injection, Eylea, 1.0 mg]), unclassified biologics (HCPCS code J3490 or 3590), or any combination of these medications. Participants were classified by the injection they received most, and if there was a tie, they were randomized solely to one medication group or the other. This simple classification may have minimized inter-anti-VEGF therapy differences, and attenuated the results of my drug-specific investigations towards null.

Demographic variables

_age, birth year, sex, geographic region, year of inclusion in the study

Healthcare resource use

_insurance type (commercial or Medicare)

_days spent in hospital

Anti-VEGF injection-related variables

_type of injection – Lucentis, Avastin, Eylea,

_number of injections in period under study

Comorbidities in the last 365 days

_ICD-9 codes

_Disease name

_Frequency of visits for disease

Concomitant medications dispensed in the last 90 days

_ National Drug Code Directory (NDC) codes

_ Drug name

_ Route of administration

_ Frequency

_ Dosage

POTENTIAL CONFOUNDERS

The clinical and lifestyle factors of hyperlipidemia (OR 3.25 [95%CI 2.81-3.76]), smoking (OR 2.87 [95%CI 2.58-3.19]), diabetes (OR 2.37 [95% CI 2.07-2.71]), hypertension (OR 1.91 [95%CI 1.74-2.10]), and abdominal obesity (OR 1.62 [95% CI 1.45-1.80]) are known modifiable risk factors for the occurrence of AT events in the general population world-wide (Previtali, Risk factors for venous and arterial thrombosis., 2011).

Potential risk factors for nvAMD across the Rotterdam, Beaver Dam and Blue Mountains eye study included: current smoker (OR 4.55 [95% CI 2.74,7.54[), underweight, ie, basal metabolic index<20 ([OR 1.72 [95% CI 0.81,3.65]), acute MI ([OR 0.94 [95% CI 0.52,1.70]), angina ([OR 1.03 [95% CI 0.60,1.75]), stroke ([OR 1.07 [95% CI 0.55,2.08), hypertension ([OR 1.48 [95% CI 0.99,2.22]), cholesterol (per mmol/L) ([OR 1.01[95% CI 0.91,1.27]), HDL-cholesterol per mmol/L ([OR 1.19 [95% CI 0.76,1.86]) (Smith, et al., 2001). For my study, myocardial infarction and stroke were outcome variables, and there was no information about smoking. All other covariates observed as risk factors for both AT events and nvAMD were considered potential confounders.

A DESCRIPTIVE ANALYSIS OF nvAMD STUDY PARTICIPANTS

The distribution of age and gender in the nvAMD study population is shown in Figure 2-2. Participants ranged in age from 50 years through 108 years. The median age was 80 years (mean [SD] = 77.8 [10.3] years). The largest numbers of participants (70%) were in the 70-90 year age range, with nearly a quarter (22.8%) of the study population aged 80-84 years old. A total of 92,633 (60.5%)participants were female; females were statistically significantly older than males ($Median_{female}$ = 78.6, $Median_{male}$ = 76.58, Kruskal-Wallis chi-square = 1590.98, df = 1, p-value = <0.0001).

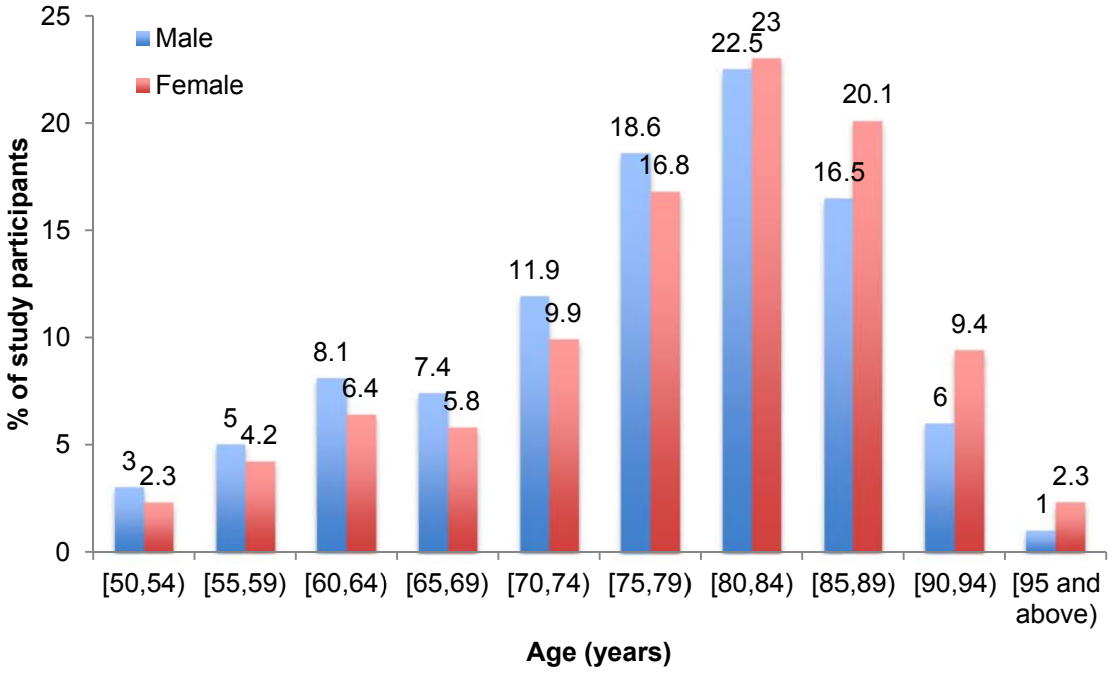

Figure 2–2. Age and gender of study participants

Almost a fourth of nvAMD study participants had an AT event after the index time at which the diagnosis of nvAMD was made (Table 2-3). The number of participants with MI event (3.0%) was much lower than the number with stroke (23.9%). A very small percentage of participants (0.16%) had both stroke and MI. In the analyses, they were classified by their diagnosis of MI as they would lend greater numerical strength in that smaller group than in the stroke group.

Table 2-2. Participants with first-time AT events during 2006-2012

MI Event	Stroke Event	N	Percent (%)
0	0	111683	73.0
1	0	4594	3.0
0	1	36501	23.9
1	1	241	0.16
Total		**153,019**	**100.0**

0 = no, 1 = yes

Table 2-3 shows the top comorbidities recorded among participants in the 365 days preceding nvAMD diagnosis. Approximately half (45.5%) of the participants were reported as having hypertension, and about a third (28.9%) with hypercholesterolemia. About a quarter had a history of cancer.

Table 2–3. Top comorbidities among participants in 365 days preceding nvAMD diagnosis

Comorbidities	Number	Frequency (%)
Hypertension	69609	45.49
Hypercholesterolemia	44163	28.86
Cancer	37940	24.79
Diabetes	26811	17.52
COPD	21100	13.79
Atrial Fibrillation	14788	9.66
History of stroke	14744	9.64
Coronary heart disease	8189	5.35
Renal disease	6825	4.46
Peripheral artery disease	6081	3.97
Autoimmune eye disease	3718	2.43
History of drug allergy	2535	1.66
History of non-drug allergy	2310	1.51
Obesity	2203	1.44
History of MI	1541	1.01
History of CABG	969	0.63
Cerebrovascular disease[a]	859	0.56
Dementia	725	0.47

CABG=cardiac artery bypass graft, COPD=chronic obstructive pulmonary disease, Dx=disease
Note: Many participants have multiple comorbidities and columns do not sum to 100%; each cell is unique in that if 53% of participants have hypertension, then 100-53=47% do not have hypertension
[a]Counted excluding AT events.

The top ten concomitant medication prescriptions dispensed in 90 days prior to nvAMD diagnosis generally corresponded with treatment for the top comorbidities (Table 2-4). Other prescriptions were filled for disorders that are commonly associated with age, such as osteoporosis and glaucoma.

Table 2-4. Top 10 medication prescriptions filled by study participants between 2006-2012

NDC Code	Medication	Indication
63653117101	Plavix	To prevent heart attacks and strokes in persons with heart disease (recent heart attack), recent stroke, or blood circulation disease
71015523	Lipitor	To prevent high blood cholesterol, high triglyceride and hyperliproteinemias
597005801	Norvasc	To treat vasospastic and chronic stable angina
13830304	Xalatan	To treat glaucoma
406035705	Ibuprofen	To treat pain (especially pain due to inflammation)
186504031	Toprol XL	To treat stable, asymptomatic heart failure of ischemic, hypertensive or cardiomyopathic origin
186109005	Nexium	To treat symptomatic gastro-esophageal reflux disease
6003144	Fosamax	To prevent osteoporosis
173069600	Advair	To treat asthma or COPD
25152531	Celebrex	To treat symptoms of osteoarthritis, rheumatoid arthritis

About 40% each of study participants were enrolled in Medicare subscription plans and Preferred Provider Organizations respectively. About 10% were enrolled in Health Management Organization type subscription plans (Table 2-5).

Table 2-5. Insurance plan subscriptions for participants in 2006-2012

Plan type	Number	Frequency (%)
Medicare-comprehensive	63863	41.73
PPO	60073	39.25
HMO	14590	9.53
Other	14493	9.47
TOTAL	153,019	100.0

HMO=health management organization, PPO=preferred provider organization

Time spent in hospital is one indicator of patient health status. A patient who spends 1 day in the hospital in the 365 days prior to nvAMD diagnosis is likely healthier than one who spends ten days. The number of days spent by nvAMD study participants ranged from zero to 35 days (Table 2-6). The median interquartile range (IQR) number of days spent in hospital by all participants was 0 (0, 0), and for participants with at least 1 day hospital stay, median (IQR) was 4 (2, 6).

Table2-6. Days spent in hospital within the 365 day period prior to the index date.

Days spent in hospital	Frequency
0	134264
1	2842
2	3095
3	3272
4	2342
5	1543
6	1185
7	897
8	672
9	527
≥10	2380
TOTAL	153019

The total number of dispensed medications in the 90 days before the date of AMD diagnosis is another indicator of patient health status. A patient to whom no medication was dispensed is likely healthier than one to whom seven medications were dispensed. A frequency plot of number of medications dispensed to nvAMD study participants in the 90 days preceding nvAMD diagnosis (Figure 2-4), showed Median (IQR) = 7 (3, 14).

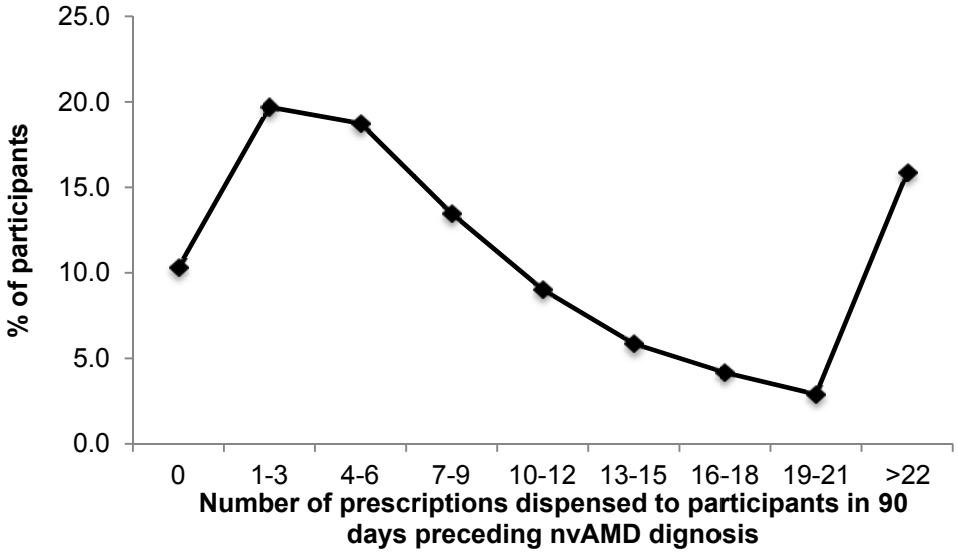

Figure 2-4. Number of prescriptions dispensed to all participants

CHAPTER THREE

Manuscript 1: "An Assessment of Risk Factors for Arterial Thromboembolic Events in Neovascular Age-Related Macular Degeneration Patients following Intravitreal Anti-Vascular Growth Endothelial Factor Inhibitor Therapy."

ABSTRACT

The purpose of my study was to identify a patient profile that can be used to determine which neovascular age-related macular degeneration (nvAMD) patients receiving intravitreal anti-vascular endothelial growth factor inhibitor (anti-VEGF) therapy, are most at risk for developing arterial thromboembolic (AT) adverse drug events. I used Cox proportional hazard models, with adjustments for selected covariates and propensity score weighting, to examine the risk factors for AT events in a retrospective cohort of 153,019 nvAMD patients from the MarketScan® database, continuously enrolled in insurance plans from 2006-2012.

My data suggested that a 3-fold increased risk of AT events in patients on anti-VEGF was associated with patient history of AT events prior to nvAMD diagnosis (Hazard ratio [HR] 3.28, 95% confidence interval 3.21, 3.38). Use of the medication Plavix (HR 1.59), diagnosis of cerebrovascular disease (HR 1.42), peripheral arterial disease (HR 1.39), diabetes (HR 1.27), or renal disease (HR 1.17) also predicted increased AT adverse event risk. Age was associated with a 1.7% increase in AT adverse event risk per year. Other covariates associated with increased risk were dementia (HR 1.08), and Preferred Provider health insurance subscription (HR 1.06).

I confirmed an increased susceptibility to AT adverse events in patients with a pre-anti-VEGF treatment history of AT events, when receiving anti-VEGF therapy for nvAMD.

INTRODUCTION

Reports of anti-vascular endothelial growth factor suppression effects such as reduced plasma vascular endothelial growth factor (VEGF) levels, and regression of neovascularization in the fellow untreated eye following unilateral anti-VEGF injection indicate that anti-VEGF enters the systemic circulation (Sharma, Ong, & Ooi, 2014) (Bakbak, 2013). The dose of anti-VEGF is about 400 times smaller than is used for systemic (intravenous therapy), and it is introduced into the physiologically restricted intravitreal compartment of the eye (Costagliola, et al., 2012). Although the concentration of anti-VEGF that reaches the systemic circulation is therefore very limited, the threshold concentration that inhibits vascular endothelial growth factor (VEGF) activity (Inhibitory Concentration-50) is in the subnanomolar range (Carneiro, Falcao, Barthelmes, & et al., 2012) (Matsuyama, Ogata, Matsuoka, Wada, Takahashi, & Nishimura, 2010) (Zehetner, 2013).

Intravitreal anti-VEGF agents are used for a population in which age and age-associated hepatic or renal insufficiency may impair metabolic clearance of drugs. Also, injections are given repeatedly and anti-VEGF and their metabolites may have a cumulative effect in the systemic circulation of members of the aging population, who are susceptible to serious systemic adverse events. Such susceptible patients may exhibit serious adverse consequences of systemic VEGF suppression at drug doses or plasma concentrations that have no adverse effects on their peers.

The profiles of participants susceptible to adverse reactions from the systemic effects of drugs such as rofecoxib, timolol, and cerivastatin were not discovered until after the drugs were on the market, since participants in regulatory pre-market studies were neither sufficient in number, nor clinically diverse enough to identify rare adverse events in the select groups of people who developed serious adverse reactions. Rofecoxib significantly increases the risk of myocardial infarction (MI) in people with a previous cardiovascular problem especially when given in doses

above 25 mg/day (Solomon D. , 2004). Timolol produces significant bronchopulmonary adverse events in patients with asthma or other bronchospastic conditions (Botet, 1986) (Van Buskirk, 1980). Cerivastatin causes rhabdomyolysis in individuals with malignant hyperthermia susceptibility (Staffa, Chang, & Green, 2002) (Lucas, Weathersby, Rocco, Pepper, & Butler, 2002).

My study investigated risk factors for non-fatal arterial thromboembolic (AT) adverse event occurrence from infiltration of the systemic circulation from anti-VEGF in regular clinical practice. It is difficult to examine a profile for the context of actual clinical care through early phase regulatory studies and clinical trials, since there are considerable differences between patients selected for clinical trials, and patients in the regular population. Clinical trials also tend to focus on an inadequate time-span to recognize long-term adverse events in potentially susceptible patients.

The very large commercial MarketScan® patient database analyzed for my study is representative of the insured US population, and is sufficiently powered to identify susceptible participants by investigating interactions with comorbidities, concomitant medications, and other important factors, even for low-rate adverse events.

SPECIFIC AIM AND HYPOTHESIS

The goal of my study was to assess pre-existing patient characteristics that may be risk factors for occurrence of potentially fatal arterial thromboembolic events (ie, non-fatal stroke and non-fatal MI) following anti-VEGF therapy for nvAMD in regular clinical practice.

Null hypothesis: Risk factors associated with the use of VEGF inhibitors in the treatment of nvAMD contribute equally to AT event occurrence in participants treated with anti-VEGF.

METHODS

Cohort study definition

In a cohort study a group of individuals is followed over time and their exposure to an intervention (in this case, anti-VEGF), is determined in order to compare the average risks, rates and occurrence times of the outcome of interest (in this case, AT events) in the exposed and unexposed groups [Rothman 3rd edition]. The relative risk can be used to assess whether anti-VEGF and AT events are causally linked. Based upon the assumption that the AT adverse event risk for anti-VEGF and other covariates were constant throughout the study period, I used Cox proportional hazard models to estimate the hazard ratios (interpretable as risk ratio or relative risk).

I selected the cohort study method because cohort studies have several advantages. They are less prone to confounding and biases than are case-control studies. The direction of causality is more easily established in a cohort than a case-control study since a plausible temporal relationship can be observed in the study. Long-term cohort studies can detect delayed effects, drug interactions, influences of multiple disease processes on drug effects, and the effect of aging in response to drugs (Juergens 1985).

Cohort studies are usually time-consuming, labor-intensive, and expensive; however, since mines was a retrospective cohort study using information from an insurance claims database, it has none of these disadvantages. Ideally, the whole cohort should remain at risk and under observation for the whole follow-up time period, and loss to follow-up and competing risk must be minimized. In my database study, a closed cohort effect was easily achieved by restricting participation to persons who were continuously enrolled in the period 2006-2012, and close monitoring was achievable since insurance claims had to be filed for reimbursement.

Propensity scoring definition

My study participant assignment of anti-VEGF treatments was shaped by clinical judgment and patient/physician preference. The resultant systematic differences between persons who received anti-VEGF and those who did not, constitutes a selection bias (ie, confounding by indication). In an attempt to balance the differences between treated and untreated participants that may have contributed to treatment decisions, I created a propensity score (Appendix II). In propensity scoring the conditional probability of receiving a treatment (ie, anti-VEGF) given observed covariates is estimated, and the estimate balances the differences for the covariates used to create the score (Rosenbaum and Rubin 1983). In a cohort study stratifying treated and untreated participants on a single variable, the propensity score tends to balance all of the observed covariates but importantly, it cannot balance unmeasured covariates.

I regressed patient treatment status (anti-VEGF [yes/no]) on all of my measured baseline covariates such as insurance plan type, concomitant medications (ie, Norvasc, Plavix, Lipitor, Crestor, Tricor, Toprol, Xalatan), comorbidities (ie, history of AT event, history of stroke, history of MI, history of drug allergy reaction, history of non-drug allergy reaction, record of cardiovascular disease [CVD], chronic obstructive pulmonary disease [COPD], coronary heart disease [CHD], dementia, atrial fibrillation, history of coronary artery bypass graft [CABG], cancer, renal disease, diabetes, hypertension, peripheral arterial disease, obesity, and hypercholesterolemia), date of nvAMD diagnosis, age at nvAMD diagnosis, total medications in the 90 days before nvAMD diagnosis, number of hospital days in the year prior to nvAMD diagnosis, and number of hospital visits in the year prior to nvAMD diagnosis (Austin, 2011). I used a generalized additive model to allow non-linear effects of continuous variables like age and date of diagnosis. The resulting propensity score was the predicted probability of treatment derived from the fitted regression model, and I incorporated the score into my assessments of the association of anti-VEGF with AT events, using the inverse probability of treatment

weighting (IPTW) method (D'Agostino, 1998).

STATISTICAL ANALYSIS

I followed up all of the participants from the date of first recorded nvAMD diagnosis until time-to-AT event, or up until their last recorded service date before the end of the study on December 31, 2012. I performed Cox proportional hazard regression with the outcome variable AT event as the status variable and "time-to-first-event" as the time variable, to identify risk factors that would jointly predict higher risk of AT events. Potential predictors (covariates) were age at nvAMD diagnosis, gender, number of days spent in hospital in a 365-day period prior to nvAMD diagnosis, number of hospital visits, number of medication prescriptions filled in a 90-day period prior to nvAMD diagnosis, insurance plan type, most common concomitant medications, history of AT event, history of allergic drug reaction, history of non-allergic drug reaction, history of autoimmune eye disease, and history of comorbidities - diabetes mellitus, hypertension, hypercholesterolemia, MI, congestive heart failure, atrial fibrillation, cerebrovascular accident, dementia, cancer, COPD, peripheral vascular disease, renal disease, and total number of anti-VEGF treatments.

I tested five models: model 1, an unadjusted model; model 2, adjusted for the propensity score weights; model 3, adjusted for propensity score weights and all of the potential predictors; model 4 was an investigation to see if there was a role for interaction. Model 5, the final model, adjusted for propensity score weights and relevant variables, was selected by a backward stepwise selection process from the full model using Akaike information criteria (AIC) defined as $2k - 2\ln(\text{Likelihood})$, where k is the number of parameters in the model. I presented my results as hazard ratios and 95% confidence intervals (CI), and defined statistical significance as $P < 0.05$.

RESULTS

My cohort consisted of 153,019 newly-diagnosed nvAMD patients identified from the MarketScan® database, who were continuously enrolled in 2006-2012 (Figure 3-1). About half of my study participants (49.6%) received anti-VEGF therapy, and about a quarter (27.0%) of the study participants had AT events after their first recorded nvAMD diagnosis. The mean age in my study population was 77.0 (standard deviation, 10.3) years, and they were predominantly (60.5%) female.

Table 3-1 shows my results for Cox regression models of prognostic factors in 153,019 study participants who were continuously enrolled in the MarketScan® insurance database 2006-2012. Results for each of the regression models are included in Appendices III and IV. Univariate analysis showed no significant association of AT events with anti-VEGF. When I adjusted for age, and adjusted for clinical judgment and patient/physician preference using propensity scores with inverse probability of treatment weighting (IPTW), I found a statistically significant association (HR 1.04, 95% CI 1.02,1.05).

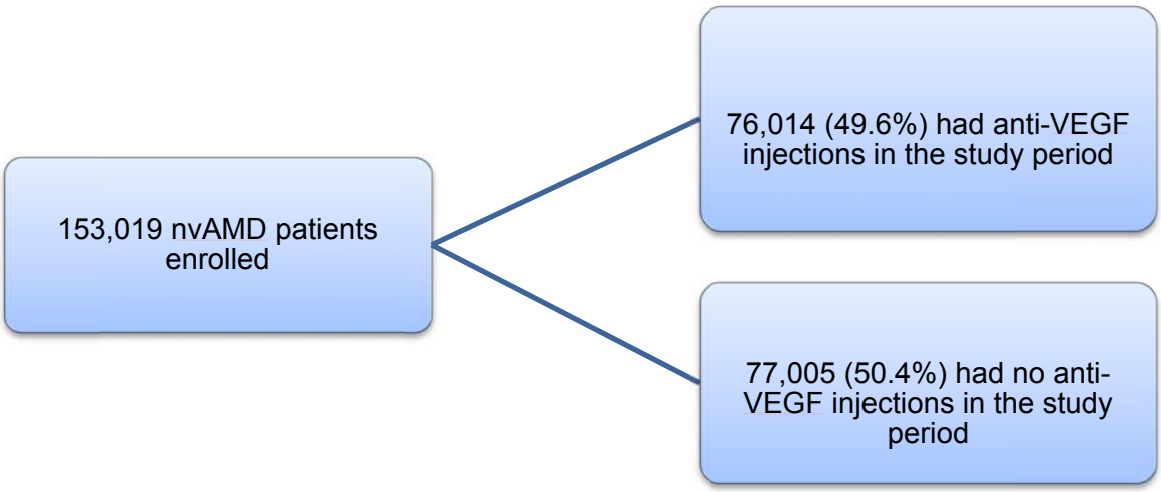

Figure 3-1. Treatment characteristics for patients enrolled in the study.

Table 3-1. Risk factor selection by Cox proportional hazard analysis for AT events associated with anti-VEGF treatment in nvAMD patients, 2006-2012 (N=153,019)

	Unadjusted		IPTW Adjusted		IPTW+Covariate Adjusted		Adjusted for Interactions		Final Model	
Factor	HR	LL, UL	HR	LL, UL	HR	LL, UL	HR	LL, UL	HR	LL, UL
anti-VEGF										
No	Reference									
Yes	1.01	0.98, 1.03	1.04	1.02, 1.05	1.16	1.14, 1.18	0.34	0.15, 0.75	0.29	0.14, 0.6
Age (year)			1.17	1.15, 1.18	1.17	1.15, 1.18	1.17	1.15, 1.18	1.17	1.15, 1.18
Plavix										
No	Reference									
Yes					1.49	1.45, 1.54	1.62	1.56, 1.68	1.59	1.54, 1.65
AT event history										
No	Reference									
Yes					3.08	3.03, 3.14	3.27	3.19, 3.35	3.28	3.21, 3.35
Cerebrovascular disease										
No	Reference									
Yes					1.37	1.28, 1.46	1.4	1.3, 1.52	1.42	1.32, 1.53
Atrial fibrillation										
No	Reference									
Yes					1.16	1.14, 1.18	1.15	1.12, 1.19	1.14	1.12, 1.17
Diabetes										
No	Reference									
Yes					1.22	1.2, 1.24	1.26	1.23, 1.29	1.27	1.24, 1.3
Peripheral arterial disease										
No	Reference									
Yes					1.41	1.37, 1.45	1.39	1.34, 1.44	1.39	1.36, 1.43
Coronary heart disease										
No	Reference									
Yes					1.17	1.14, 1.2	1.03	0.98, 1.09	1.16	1.13, 1.18
Renal disease										
No	Reference									
Yes									1.17	1.13, 1.21

HR=hazard ratio, IPTW=inverse probability of treatment weighting, LL=lower limit, UL=upper limit
NOTE: Full report of analysis regression models are provided in the appendices

Study participants with a history of AT events before their nvAMD diagnosis were three times more likely to have an AT event (HR 3.08, 95% CI 3.03, 3.14) than were participants who did not have an AT event history, after I made adjustments for propensity score weights and all of my baseline covariates. Five of the 32 baseline covariates (ie, use of the medication Plavix, a recorded diagnosis of cerebrovascular disease, peripheral arterial disease, diabetes, or renal disease) were significantly associated with an increased risk of AT events in the regression. There was also a 1.7% increase in AT event risk per year associated with anti-VEGF therapy. Hypertension and hypercholesterolemia were associated with increased AT event risk in study participants on anti-VEGF, but less strongly associated than the other five risk factors.

I introduced cross-product terms to see if there was a role for interaction of any baseline covariates with anti-VEGF (Table 3-2). Arterial thromboembolic adverse event risk was significantly reduced in anti-VEGF-treated participants who had been dispensed Plavix, and those who had been dispensed Xalatan compared with those anti-VEGF-treated patients who were not dispensed either of these medications. A history of CABG or previous AT event, or a recorded diagnosis of cerebrovascular disease were also significantly associated with reduced AT adverse event risk with anti-VEGF in comparison with participants who did not have such history or recorded diagnosis.

Table 3-2. Results of logistic regression of selected covariates for interactions

with anti-VEGF

INTERACTION COVARIATE	ODDS RATIO	95% CONFIDENCE INTERVAL (LL, UL)
anti-VEGF:CABG	0.71	0.59, 0.86
anti-VEGF:PLAVIX	0.89	0.84, 0.94
anti-VEGF:XALATAN	0.83	0.76, 0.91
anti-VEGF:AT HX	0.83	0.80, 0.86
anti-VEGF:CVD	0.84	0.74, 0.95

AT HX=positive AT event history, CABG=coronary artery bypass graft, CVD=cerebrovascular disease, LL=lower limit, UL=upper limit

The covariates that appeared to impact AT adverse event risk the most were a history of AT events prior to nvAMD diagnosis (HR 3.28, 95% CI 3.21,3.35), use of the medication Plavix (HR 1.59, 95% CI 1.54,1.65), cerebrovascular disease (HR 1.42, 95% CI 1.32,1.53), a history of peripheral arterial disease (HR 1.39, 95% CI 1.36,1.43), diabetes (HR 1.27, 95% CI 1.24,1.30), renal disease (HR 1.17, 95% CI 1.13,1.21), age at AMD diagnosis (HR 1.17, 95% CI 1.15,1.18), coronary heart disease (HR 1.16, 95% CI 1.13,1.18), and atrial fibrillation (HR 1.14, 95% CI 1.12,1.17) (Table 3-3).

Table 3-3. List of impactful risk factors for AT events in association with anti-VEGF

Variable	HR estimate	95% CI (LL,UL)

Anti-VEGF	0.296	0.146, 0.602
AT event history	3.28	3.21, 3.35
Plavix	1.59	1.54, 1.65
Cerebrovascular disease	1.42	1.32, 1.53
Peripheral arterial disease	1.39	1.36, 1.43
Diabetes mellitus	1.27	1.24, 1.30
Renal disease	1.17	1.13, 1.21
Age at AMD diagnosis	1.17	1.15, 1.18
Coronary heart disease	1.16	1.13, 1.18

AMD=age-related macular degeneration, AT=arterial thromboembolic, CI=confidence interval, HR=hazard ratio, LL=lower limit, UL=upper limit

DISCUSSION

My data showed a 3-fold increase in risk of AT events in association with a history of AT event before nvAMD diagnosis, for study participants who received anti-VEGF. I confirmed the association suggested by Genentech's announcement letters reporting observations on the anti-VEGF, Lucentis, in a regulatory trial. In an interim data analysis in the SAILOR (Safety assessment of intravitreal Lucentis for nvAMD) clinical trial, a dose response in the form of a higher incidence of stroke with the higher dose of Lucentis (1.2% in the group treated with 0.5 mg Lucentis vs. 0.3% in the group treated with 0.3 mg) was observed especially in participants with a prior history of AT events (Boyer, Heier, Brown, Francom, Ianchulev, & Rubio, 2009). The difference disappeared after six months.

My study showed too, that patients on Plavix have 60% increased risk of developing AT events in association with anti-VEGF. Plavix (Clopidogrel) is an oral, thienopyridine-class antiplatelet agent prescribed to prevent heart attacks and strokes in persons with heart disease

(recent heart attack), recent stroke, or blood circulation disease. Clearly, filling out a Plavix prescription indicates ongoing treatment of a clinically observable susceptibility to AT events.

Peripheral arterial disease, coronary heart disease and cardiovascular disease were significantly associated with increased AT adverse event risk in participants who received anti-VEGF therapy. Their contribution can occur by multiple interrelated paths. Faulx, et al observed that patients with cardiovascular disease are particularly vulnerable to adverse drug reactions due to their advanced age, polypharmacy, and the influence of heart disease on drug metabolism (Faulx & Francis, 2009).

I identified renal disease, adult-onset diabetes, and atrial fibrillation as other risk factors for AT adverse events in nvAMD patients undergoing anti-VEGF therapy. Renal disease has been described as affecting drug handling, and PirMohamed, et al observed that renal disease renders patients more likely to have pharmacological reactions (Pirmohammed, James, & Meakin, 2004). Additionally, renal disease affects the likelihood of anemia as well as the effectiveness of the coagulation pathways. Huri, et al observed that diabetes patients are at increased risk for experiencing drug-related problems since they often receive multiple medications and have multiple comorbidities (Huri & Fun Wee, 2013).

Arterial thromboembolism is described as the most serious common complication of atrial fibrillation, and the most clinically evident thromboembolic event is the AT event, cerebral ischemic stroke (The Euro Heart Survey on Atrial Fibrillation, 2010). In a systematic review and meta-analysis of 17 studies, the overall prevalence of cerebral ischemic lesions detected by magnetic resonance imaging, and by computed tomography among patients with atrial fibrillation was 40% and 22%, respectively (Kalantarian, Ay, & Gollub, 2014). In a study by Manning, et al, atrial fibrillation was associated with more than a two-fold increased risk of cerebral ischemia in patients with no history of symptomatic stroke (OR, 2.62; 95% CI 1.81-

3.80) in 11 studies. It is no surprise that renal disease, diabetes, or atrial fibrillation were identified as predisposing factors for AT adverse drug events in my Cox regression.

The combined effect of increased chronic disease burden and loss of physiologic reserve makes the aging population particularly susceptible to adverse drug events and the effect increases significantly with age (Budnitz, 2006). For the very old population (70 years or older), Budnitz, et al described hospitalization rate for adverse drug events to be 3.5 times higher for the older population than for those aged 65 to 69 years (Budnitz, Lovegrove, Shebab, & Richards, 2002). Aging affects all of the pharmacokinetic stages (ie, absorption, distribution, metabolism and excretion). Additionally, aging is associated with changes in receptor sensitivity that alter cellular response to drugs.

Age was associated with increased AT event risk in my study. Elderly people have more comorbidities, as a result they are seen by multiple health care workers who prescribe multiple drugs. The result of such polypharmacy is an increased likelihood of pharmacologic drug reactions. The likelihood of developing an adverse interaction increases with the number of drugs prescribed (Atkin & Shenfield, 1995). Patients with coronary heart disease or other cardiovascular disorders have been described as taking seven medications each, on average. Taking seven medications concurrently gives the potential for 6+5+4+3+2+1=21 drug-drug interactions.

An important advantage that I had in investigating multiple covariates to assess risk factors in this study was the large size and clinical heterogeneity of the MarketScan® database patient population. Stein, et al observed that any source other than a database usually provides an inadequate sample size of people with particular conditions or outcomes of interest to permit adjustment of many confounding variables in multivariable models (Stein, Lum, Lee, Rich, & Coleman, 2014).

I faced certain limitations in the conduct of this study. Diagnoses of the study outcome, AT events, and of participant comorbidities were obtained from insurance claims data, and could not be verified. Disease misclassification or ICD-9 miscoding may have occurred. Either of these biases is unlikely to have affected exposed and non-exposed participants differently, so any misclassification bias will be nondifferential and give rise to attenuation of my estimates of effect towards the null.

Measurement of the exposure, intravitreal anti-VEGF therapy was also from insurance claims data, and any measurement errors would affect only participants who were exposed to anti-VEGF. Any resulting bias would affect my effect estimates and can bias them away from or toward the null depending on if the error increases the frequency of anti-VEGF or decreases it.

In conclusion, a history of AT events prior to nvAMD diagnosis, prescribed treatment with Plavix, presence of cerebrovascular disease, history of peripheral arterial disease, diabetes, renal disease, older age at nvAMD diagnosis, presence of coronary heart disease, and presence of atrial fibrillation, are risk factors associated with the occurrence of potentially fatal AT events (ie, non-fatal stroke and non-fatal MI) following anti-VEGF therapy for nvAMD in regular clinical practice. The results of my study suggest that nvAMD patients should be screened specifically for these factors before commencing intravitreal anti-vascular endothelial growth factor therapy.

CHAPTER FOUR

Manuscript 2: "A Study of Arterial Thromboembolic Events Associated with any Intravitreal Anti-Vascular Growth Endothelial Factor Inhibition Therapy in Regular Clinical Practice."

ABSTRACT

The purpose of this study was to examine the odds of arterial thromboembolic (AT) events associated with any intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy. Most information on anti-VEGF-associated adverse drug events comes from regulatory studies that are ethically bound to not have an unexposed control group and whose treated patients are carefully selected without measurements of drug adverse events as a primary study aim.

In insurance claims data from 153,019 nvAMD patients from the MarketScan® database, I assessed the association of the rare AT event outcomes of stroke and myocardial infarction with anti-VEGF by conditional logistic regression. Of the total number, 41,336 (27.0%) participants had AT events while they were continuously registered during the period 2006-2012 and 76,014 (49.7%) of the total participants received anti-VEGF in the same time frame.

Intravitreal anti-vascular endothelial growth factor inhibitor therapy appeared to have a 20% protective effect against AT adverse drug event (Odds ratio 0.79; 95% Confidence interval 0.77, 0.81), in a model adjusted for potential confounders. The confounders included age at nvAMD diagnosis, gender, patient health status indicators (ie, number of days spent in hospital in 365 days preceding first recorded AT event diagnosis, number of medication prescriptions filled in 90 days before AT event diagnosis date), history of AT events, and the top ten comorbidities.

When I included patient time in the study and propensity score weights in the logistic regression, the apparent protective effect was removed, and odds ratio was 1.18 (95% CI 1.16, 1.2),

indicating 18% increased odds of AT events in association with anti-VEGF therapy. The change in direction and magnitude of effect with consideration of patient time and propensity score weighting suggested a positive, time-varying effect of anti-VEGF association with AT adverse drug events that is influenced by physician preference and clinical judgment.

My analysis provided a valuable illustration of the importance of patient-time on study and confounding by indication, when interpreting insurance claims data for AT adverse events following anti-VEGF therapy.

INTRODUCTION

Michels, et al presented the report of a case-series (abstract number FP-FR-18-5) at the 2014 World ophthalmology Congress. (Michels, 2005) In their study, patients with neovascular age-related macular degeneration (nvAMD) received two treatments, one month apart, of either Lucentis 0.5 mg or Avastin 1.25 mg. Untreated patients with atrophic AMD served as the comparison group. The two-injection regimen was completed by 13 patients in each of the treatment groups. They reported that the data safety monitoring committee stopped the study early after three thromboembolic events occurred in the treatment group. One event was a fatal stroke, another event was reported as pulmonary embolism, and the last event was a suspected transient ischemic attack. There were no similar events in the comparison group. While the numbers in this case series are clearly insufficient to draw any conclusions, it is an example that serves as a call for additional scientific investigation of adverse events in anti-vascular endothelial growth factor (VEGF) therapy. The findings from Michels' case series are in line with the results of Ueta's investigation (Ueta, Mori, Kunimatsu, Yamaguchi, Tamaki, & Yanagi, 2011). Ueta, et al evaluated periodic magnetic resonance imaging scans of 63 patients with nvAMD who had no history of symptomatic stroke or myocardial infarction (MI) in six months preceding initiation of anti-VEGF. They found new asymptomatic stroke lesions in two out of 27

patients who were treated with three to four monthly anti-VEGF treatments in the six-month period.

While arterial thromboembolic (AT) events are rare, they are very important because they are potentially fatal. Furthermore, the at-risk groups for anti-VEGF treatments are elderly and elderly persons have an underlying predisposition for AT events. Efforts to investigate adverse events associated with anti-VEGF are usually included a secondary objective in clinical trials. Clinical trials, limited by insufficient statistical power and study time interval, are unable to adequately test for clinically relevant differences in rare adverse events. They are undertaken for regulatory purposes and the patients selected for participation are different than the patients seen in a regular clinical practice. My study is an investigation of the association of AT events with anti-VEGF in a regular clinical practice setting, using insurance claims data from 153,019 nvAMD patients in the nationally representative MarketScan® database, who were continuously enrolled in 2006-2012.

SPECIFIC AIM AND HYPOTHESIS

To estimate the odds of nonfatal AT events following anti-VEGF therapy for nvAMD in regular clinical practice.

Null hypothesis: There is no difference in the odds of occurrence of AT events between nvAMD participants who receive anti-VEGF and those who do not.

METHODS

Case-control study definition

The intent of a case-control study is to determine the degree of association between an exposure (in this case anti-VEGF) and an outcome of interest, which in this case is AT adverse drug events. The study compares participants who experience AT events, also known as "cases", with another group who are sampled from the same source population (in this case the

MarketScan® database) independent of their exposure to anti-VEGF, and who do not experience AT events. This latter group is known as “controls”. The ratio of odds of exposure to anti-VEGF is calculated as a measure of association. Ideally, the distribution of covariates in the source population is such that cases and controls are very similar in all aspects (eg, age, sex, race, treatment variables) except in their treatment with anti-VEGF. Elimination of the (confounding) differences by restriction, stratification or analytic methods makes it possible to describe an association of anti-VEGF and AT events with greater certainty (Rothman, Greenland, & Lash, 2008).

I chose a case-control design to enable comparison with the odds ratio effect measure in previous investigations of this topic. Case-control studies have several advantages. They can be used to study rare outcomes such as AT adverse drug events because they selectively recruit persons with the outcome of interest. They can also be used to assess confounding factors. Other advantages of case-control studies did not apply since mines was a database population study. Case-control studies require fewer participants than do cohort studies, and as a result are less expensive and can be conducted in a shorter time frame. Since participant outcomes are studied retrospectively, there is usually little risk to participants (Armenian, 2009). However, case-control studies are more prone to confounding and biases than are cohort studies. Essentially, the association observed in a case-control study is an outcome of a causal mechanism rather than the cause itself and cannot be interpreted as causal.

Definition of Cases

I defined Cases as nvAMD participants with an ICD-9 diagnosis of non-fatal MI, non-fatal stroke, or both events after the diagnosis of nvAMD.

Definition of Controls

I defined Controls as nvAMD participants who had no record of non-fatal MI or non-fatal stroke in the period under study (ie, from the time of diagnosis of nvAMD until the last recorded visit before December 31, 2012). They were selected as incidence-density controls having a date of diagnosis within 30 days of date of diagnosis of a corresponding case in order for the computed odds ratio to estimate a rate ratio.

Anticipated biases for case-control study and their solutions

In general, nvAMD participants were seen at least monthly while they were in treatment. Participants in a regular anti-VEGF therapeutic regimen are watched more closely, and clinicians are more likely to suspect an AT event than in participants who are not being so closely monitored. This differential ascertainment bias could cause us to overestimate the effect of anti-VEGF. To prevent overestimation, my analysis included a comparison of frequency of Cases' and Controls' physician visits, in addition to including the number of visits as a variable in multivariate analysis.

A more complete treatment record may have been obtained from Cases who did not have a successful anti-VEGF treatment outcome, or who developed complications, compared with persons who had a successful anti-VEGF treatment outcome. That would constitute a differential information bias. Also, important details about exposure to therapy or intervention such as frequency, dose, and skipping patterns may have been missed in AT event controls that had anti-VEGF. These information bias could cause either over- or under-estimation of the odds ratio. One way to explore the bias would be subgroup analysis, performed by reviewing hospital charts for information available for a subset of participants. The MarketScan® database is de-identified and secondary analysis was not possible. The bias could also be investigated using sensitivity analysis methods.

I selected participants on the basis of continuous enrollment over a year-long period. While this provided a closed study population for ease of analysis, it excluded participants who were lost to follow-up during the year, and there was no information available about the reason for their dropout. Their non-enrollment may conceivably have been related to financial or to health issues and either of these may have given rise to a differential selection bias if more Cases than Controls dropped out due to poor health or inadequate finances. The selection bias could be explored by validating the data using sub-group analysis testing methods. That method would have require returning to individual hospitals to attempt to verify the information provided, but MarketScan® data has been very carefully de-identified to prevent such action.

STATISTICAL ANALYSIS

Exploratory analysis

In an exploration of the data, I tested Case and Control groups for differences in means between discrete variables such as age, number of comorbidities, number of concomitant medications, and days spent in the hospital in the 365 days preceding nvAMD diagnosis, using t-test of means. I also tested differences between medians for categorical variables such as sex using chi square tests. In logit-transformed locally weighted scatterplot smoothing (Loess curves), I graphed the log-odds of AT events against known covariates to determine if their relationships were linear or otherwise. I also examined the relationships between AT events and potential confounders using the Mantel-Haenszel method to confirm the role of confounders.

Case-Control analysis

I used logistic regression to analyze the odds of AT events in association with intravitreal injection. I compared the proportion of participants who received anti-VEGF therapy in the Case and Control groups to those who did not receive therapy. I included both linear and quadratic terms for age in years, at the time of the first recorded nvAMD diagnosis, based on the result of exploratory analyses, and female was set as the reference in the gender group. I included both

linear and quadratic terms for the number of hospital visits based on exploratory analyses. I set absence of the risk factor as a reference category for comorbidities and no filled prescriptions as a reference category for each of the concomitant medications.

I created a propensity score to account for baseline covariate differences among the treated and untreated patient groups. I included all of the baseline covariates, which were determined from data prior to the diagnosis of nvAMD, in the propensity score. These included insurance plan type, concomitant medications (ie, Norvasc Plavix Lipitor Crestor Tricor Toprol Xalatan), comorbidities (ie, history of AT event, history of stroke, history of MI, history of drug and non-drug allergic reaction, and the comorbidities of cerebrovascular disease [CVD], chronic obstructive pulmonary disease [COPD], congestive heart disease [CHD], dementia, atrial fibrillation, history of coronary artery bypass graft [CABG], cancer, renal disease, diabetes, hypertension, peripheral arterial disease, obesity, and cholesterolemia) and allowing non-linear smooth terms for continuous variables, date of AMD diagnosis, age at AMD diagnosis, total number of medication prescriptions filled in the 90 days before AMD diagnosis, number of hospital days in the year prior to AMD diagnosis, and number of hospital visits in the year prior to AMD diagnosis.

I examined six models. In the first (unadjusted) model 1, no adjustment was made for confounders. In model 2, adjustment was made for potential confounders which included age, gender, patient health status indicators (ie, number of days spent in hospital in 365 days preceding first recorded AT event diagnosis, number of medication prescriptions filled in 90 days before AT event diagnosis date), number of visits for injections, history of AT events, and the top ten comorbidities. In model 3, an adjustment was made using the propensity score as inverse probability of treatment weights. Since history of AT events was the strongest predictor of AT event risk in my other investigations in this study population, in model 4, adjustment was made for both propensity score and AT event history. In model 5, patient time on the study was

included in the adjustment, and in model 6, regression analysis was performed independently for MI and stroke that were the two components of AT events of interest for our study.

RESULTS

There were 153,019 nvAMD patients continuously enrolled in the MarketScan® database between 2006 and 2012 (Figure 4-1). My Cases comprised 41,336 persons (27% of all study participants) who had AT adverse events after their diagnosis of nvAMD and 44% of these AT adverse event Cases had claims records showing they had anti-VEGF therapy. The Controls comprised the 73% of study participants (111,683 persons) who did not have recorded AT adverse events after their nvAMD diagnosis and 51% of AT adverse event Controls had claims records of anti-VEGF therapy.

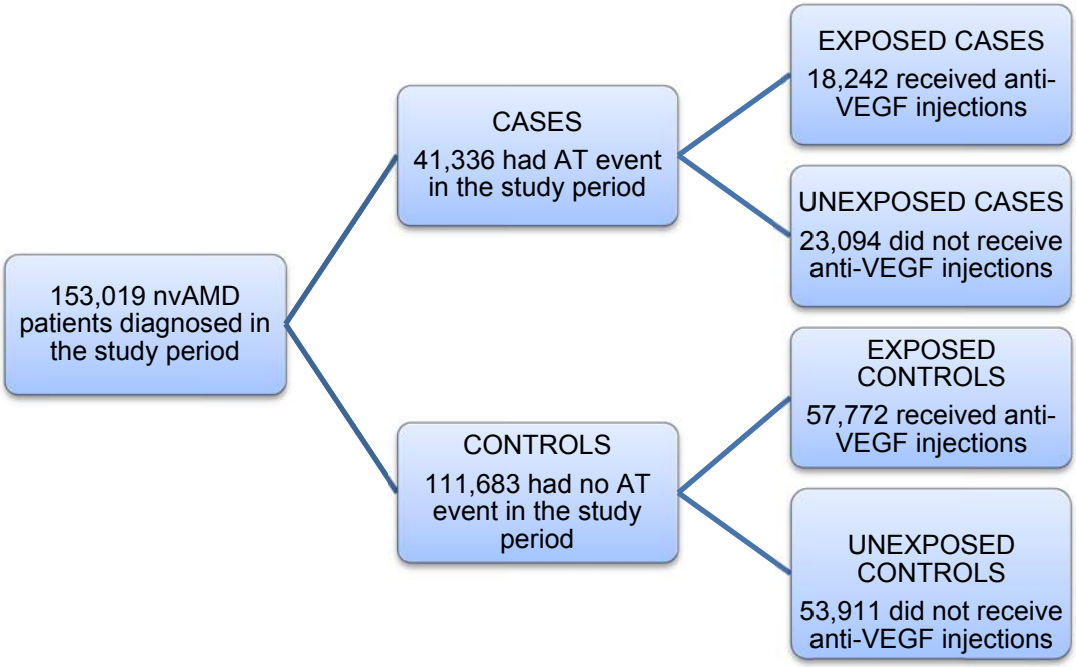

Figure 4-1. Consort diagram showing the case/control selection process

The median age of participants in the Case and Control groups was 82 years and 79 years respectively ($P < 0.001$). There were more females in the Control than in the Case group (P

<0.001). Cases spent more days in hospital in the 365 days preceding their nvAMD diagnosis and filled out more prescriptions in the 90 days before their diagnosis than did Controls (Table 4-1).

Hypertension, hypercholesterolemia, a history of prior AT event, and history of prior stroke were the most frequently observed comorbidities among participants (Table 4-2) Hypercholesterolemia and cancer were reported with similar frequency in AT adverse event Cases and Controls, but the frequencies of all other reported comorbidities were higher among Cases than Controls. Chi-square test of proportions revealed statistically significant differences between AT adverse event Cases and Controls for all comorbidities of interest except a history of non-drug allergy.

Table 4-1. Comparison of demographic variables for Cases and Controls

Variable	Cases[a] (median, IQR)	Controls[b] (median, IQR)	Test
Age – median (IQR) (at first NVAMD diagnosis)	82 (76, 86)	79 (70, 85)	Kruskal-Wallis chi-square = 3532.53, df = 1
Gender			
Female	17082 (58%)	43304 (61%)	Chi-square = 82.06, df = 1
Male	24254 (42%)	68379 (39%)	
Days spent in hospital (in 365 days prior to NVAMD diagnosis)	0 (0, 2.86)	0 (0, 0)	Kruskal-Wallis chi-square = 1158.59
Days spent on hospital in 365 days prior to NVAMD diagnosis – only for persons who spent at least one day in hospital	4.00, (2.00, 7.00)	4.00, (2.00, 6.00)	
Number of prescriptions in 90 days before NVAMD diagnosis – median , IQR	8.00, (3.00, 16.00)	6.00, (3.00, 14.00)	Kruskal-Wallis chi-square = 680.6

[a]Cases refer to participants who had had an arterial thromboembolic (AT) event
[b]Controls refer to participants who did not have an AT event

Table 4-2. Top comorbidities reported in 365 day-period prior to nvAMD diagnosis

Comorbidities	Cases[a] (frequency, %)	Controls[b] (frequency, %)	Chi square
Hypertension	20744 (50.2%)	48865 (43.8%)	502.86
Cholesterolemia	11723 (28.4%)	32440 (29.1%)	6.89
Cancer	10861 (26.3%)	27079 (24.3%)	66.47
History of AT event	9006 (21.8%)	18263 (16.4%)	7965.73
History of stroke	8570 (20.7%)	14364 (12.9%)	8008.39
Diabetes	8548 (20.7%)	99515 (8.5%)	390.53
Chronic obstructive pulmonary disease	6736 (16.3%)	6844 (6.1%)	299.04
Atrial Fibrillation	5273 (12.8%)	6174 (5.5%)	619.84
Coronary heart disease	3165 (7.7%)	5024 (4.5%)	593.51
Peripheral artery disease	2623 (6.4%)	4477 (4.0%)	833.85
Renal disease	2348 (5.7%)	3458 (3.1%)	197.44
History of drug allergy	755 (1.8%)	1785 (1.6%)	9.88
History of MI	710 (1.7%)	1780 (1.6%)	285.86
History of non-drug allergy	627 (1.5%)	1683 (1.5%)	0.01
Cerebrovascular disease[c]	453 (1.1%)	831 (0.7%)	288.57
Obesity	418 (1.0%)	770 (0.7%)	72.86
Dementia	238 (0.6%)	487 (0.4%)	12.19
History of CABG	199 (0.5%)	407 (0.4%)	20.42

CABG=coronary artery bypass graft, MI=myocardial infarction

Note: Many participants had multiple comorbidities and columns do not sum to 100%; however, each cell is unique in that if 53% of cases have hypertension, then 100-53=47% of cases do not have hypertension

[a]Cases refer to participants who had had an arterial thromboembolic (AT) event

[b]Controls refer to participants who did not have an AT event

[c]Counted excluding AT events

About a quarter of the Cases (23.42%) had no comorbidities, while almost a third of Controls (31.11%) had no comorbidities (Table 4-3). The difference in number of comorbidities between

cases and controls was statistically significant (Kruskal-Wallis chi-square = 2668.52, df = 1, p-value = < .00001).

Table 4-3. Total number of comorbidities reported for Cases and Controls

Number of recorded comorbidities	Cases[a] (N)	Frequency (%)	Controls[b] (N)	Frequency (%)
0	9680	23.42	34749	31.11
1	7815	18.91	25009	22.39
2	7470	18.07	22505	20.15
3	6091	14.74	14887	13.33
4	4402	10.65	7839	7.02
>4	5878	14.22	6694	6.0
TOTAL	41,336	100.0	111,683	100.0

[a]Cases refer to participants who had had an arterial thromboembolic (AT) event
[b]Controls refer to participants who did not have an AT event

About half of the AT adverse event cases in my study enrolled in Medicare-comprehensive plans, and about a third of cases in preferred provider organizations (PPOs) (Table 4-4). In contrast, about 40% of controls enrolled in Medicare comprehensive, and about 20% in PPOs.

Table 4-4: Comparing plan types for nvAMD Cases and Controls

Plan type	Cases[a] (N)	Controls[b] (N)	Total (N)	Frequency (%) who had AT event
Medicare-comprehensive	20543	43320	63863	32.2
HMO	3315	11275	14590	22.7
PPO	14403	45670	60073	24.0
Other	3075	11418	14493	21.2
TOTAL	41,336	111,683	153019	27.0

HMO=Health management organization, PPO= Preferred provider organization
[a]Cases refer to participants who had had an arterial thromboembolic (AT) event
[b]Controls refer to participants who did not have an AT event

Exploratory analysis

The logit-transformed locally weighted scatterplot smoothing (Loess) function fits a nonparametric regression curve to a scatterplot. I used Lowess curves to explore univariate

relationships of my study covariates with the odds of AT events preparatory to logistic regression.

Age at diagnosis

The Loess curve plot for age at nvAMD diagnosis with the log odds of having an AT event showed a clear, nonlinear relationship (Figure 4-2). A quadratic curve seemed a reasonable approximation for the relationship.

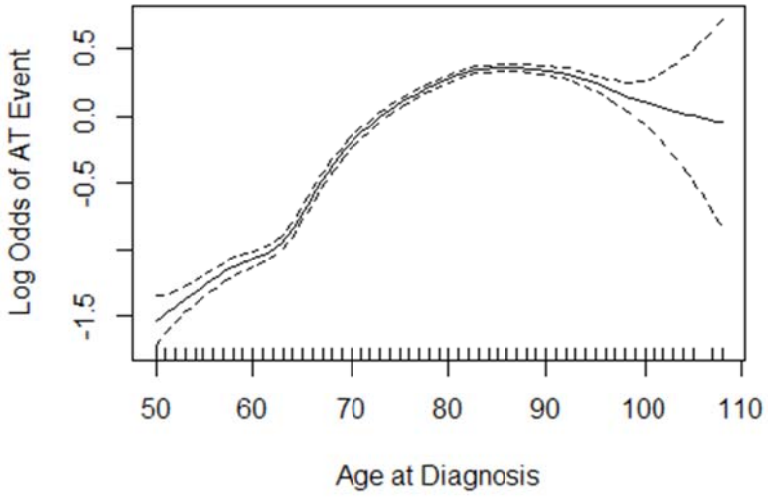

Figure 4-2. Loess curve for odds of AT event: age at diagnosis

Number of nvAMD visits

The plot for odds of AT event : number of nvAMD clinic visits (Figure 4-3) showed a slight, negative relationship between number of visits for nvAMD and log odds of an AT event.

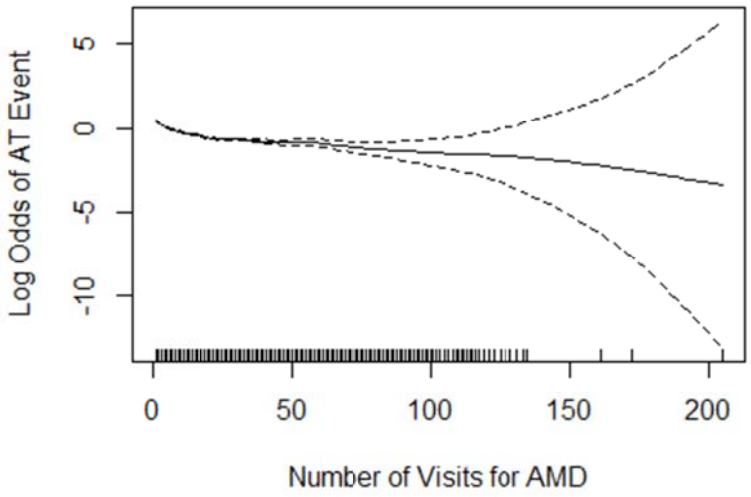

Figure 4-3. Loess curve for odds of AT event : number of nvAMD clinic visits

Number of injections

The Loess curve plot (Figure 4-4) showed a small decrease in odds of AT events with higher number of injections.

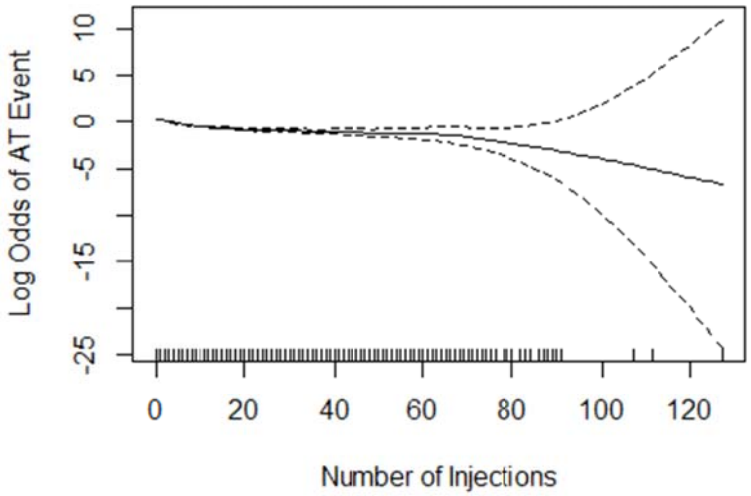

Figure 4-3. Loess curve for odds of AT event : number of anti-VEGF

Number of hospital stay days

The Loess plot for odds of AT event with number of hospital day stay in 365 days before nvAMD diagnosis (Figure 4-5) showed a complex, nonlinear association.

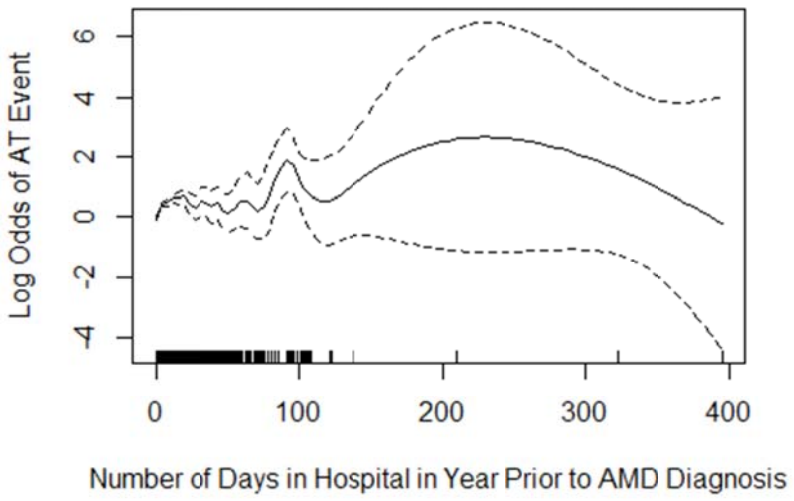

Figure 4-5. Loess curve for odds of AT event: number of days in hospital in 365 days prior to diagnosis

Association with confounders

I examined the univariate relationships between AT events with respect to anti-VEGF and potential confounders using Cochran-Mantel-Haenszel Chi-Squared Test (Table 4-5). This test checks whether the association of anti-VEGF and AT events are independent with respect to each stratum of a potentially confounding variable. In this case, all of the following variables do have a statistically significant impact on the relationship of AT events and anti-VEGF.

Table 4-5: Results of Cochran-Mantel-Haenszel Chi-Squared Test to investigate the role of confounders

Potential confounder	Mantel-Haenszel chi-square	Common odds ratio
Obesity	704.83	0.74, CI = (0.72, 0.75)
Diabetes	660.17	0.74, CI = (0.73, 0.76)
Hypertension	625.81	0.75, CI = (0.73, 0.77)
Cerebrovascular Disease	686.67	0.74, CI = (0.72, 0.76)
CHD	660.31	0.74, CI = (0.73, 0.76)
Atrial Fibrillation	665.26	0.74, CI = (0.73, 0.76)
PAD	658.86	0.74, CI = (0.73, 0.76)
Hypercholesterolemia	707.50	0.73, CI = (0.72, 0.75)
Age Group	939.49	0.70, CI = (0.68, 0.71)

CHD= coronary heart disease, PAD = peripheral arterial disease

Logistic regression

In logistic regression the unadjusted odds of having an AT event with anti-VEGF therapy was 27% lower than without therapy (Table 4-7). When I made adjustment for confounding by age at nvAMD diagnosis, gender, patient health status indicators (ie, number of days spent in hospital in 365 days preceding first recorded AT event diagnosis, number of medication prescriptions filled in 90 days before AT event diagnosis date), history of AT events, and the top ten comorbidities, the odds of having an AT event was 21% lower with anti-VEGF therapy than without therapy.

To account for time on the study, I included a patient-time covariate in the logistic regression in a quadratic form, (on the basis of the exploratory Loess graphs), and the odds of having an AT event associated with anti-VEGF became positive. The apparent “protective” effect disappeared

and there was an 8.6% increased odds of AT event occurrence for participants who received anti-VEGF compared with those who did not. I added a covariate for prior history of AT events and propensity score inverse probability of treatment weights to adjust for these confounders in my analysis, and the adjustments resulted in an 18.5% increased odds of AT events in association with anti-VEGF.

Table 4-7. Logistic regression models analysis for arterial thromboembolic events associated with anti-VEGF treatment in MarketScan nvAMD Patients, 2006-2012 (N=153,019)

	Unadjusted		Adjusted for confounding		Adjusted for patient time		Adjusted for patient time and AT event history		Adjusted for patient time, AT event history and IPTW	
Factor	OR	LL,UL	OR	LL,UL	OR	LL,UL	OR	LL,UL	OR	LL,UL
anti-VEGF										
No	Reference									
Yes	0.73	0.72,0.75	0.79	0.77,0.81	1.08	1.07,1.10	1.18	0.16,1.20	2.70	2.6,2.8
Age (year)			1.03	1.03,1.04						
Sex										
Male	Reference									
Female			0.85	0.82,0.87						
AT HX										
No	Reference									
Yes			3.73	3.47,3.74			3.2	3.1,3.3		
Cardiovascular disease										
No	Reference									
Yes			1.45	1.26,1.68						
Dementia										
No	Reference									
Yes			0.69	0.55.0.77						
Diabetes										
No	Reference									
Yes			1.26	1.22,1.30						
Peripheral arterial disease										
No	Reference									
Yes			1.35	1.28,1.43						
Coronary heart disease										
No	Reference									
Yes			1.26	1.22,1.35						

HR=hazard ratio, IPTW=inverse probability of treatment weighting, LL=lower limit, UL=upper limit
NOTE: Full report of analysis regression models are provided in the appendices

I further performed logistic regression adjusting for a history of AT events and weighted for propensity scores, separately in participants who did, and who did not receive anti-VEGF (model five). The results indicated that the odds ratio for the effect of history of AT events is higher in participants who did not (OR 3.648) than those who did receive an anti-VEGF injection (OR 2.703).

Table 4-8. Adjusted odds ratio after adding IPTW, patient time, and AT event history as covariates

	OR	LL	UL
(Intercept)	1.047	1.002	1.093
StudyDuration	0.535	0.5187	0.5519
I(StudyDuration^2)	1.044	1.04	1.049
AtHx	3.648	3.547	3.752
	OR	LL	UL
(Intercept)	4.707	4.493	4.93
StudyDuration	0.2321	0.2254	0.2391
I(StudyDuration^2)	1.149	1.145	1.154
AtHx	2.703	2.608	2.801

LL=lower limit, OR=odds ratio, UL=upper limit

DISCUSSION

The results of my population-based study suggested that overall, anti-VEGF therapies are associated with 18.6% increased odds of AT events. Change in direction of the odds ratio with inclusion of patient-time in the regression indicated that the association is a time-varying association that cannot be estimated by classic logistic regression alone.

Time was one very important factor in the analysis, but there may have been several other factors that govern the complex relationship of AT adverse events and anti-VEGF. The fact that the administration of anti-VEGF is associated with a lower AT risk suggests that unmeasured covariates may influence the decision of the clinician to offer treatment, as opposed to the AT

event risk necessarily being only an effect of the treatment itself. Likely, unmeasured covariates exist, including physician prescribing preferences, patient lifestyle factors, disease severity for comorbidities, and clinical treatment indications. For example, if an individual is impaired with their own care, has multiple negative lifestyle factors, has one or two severe systemic comorbidities, or has ocular complications that affect clinical treatment indications, a clinician may decide that the risk of a complication from the injection may override the potential benefit. Consequently that patient does not receive injections but has a higher risk for an AT event.

The bias introduced by unmeasured physician prescribing preference, could largely be removed by instrumental variable (IV) methods (Hernan & Robins, 2006). In such computation, an IV estimate of physician prescribing preference would be defined as the treatment prescribed for a single previous patient of a given physician. Physician preferences are known to vary over time and in a bid to reduce the variance inflation, an alternative IV can be estimated using a two-step method (Abrahamowicz, Beauchamp, Ionescu-Ittu, Delaney, & Pilote, 2011). First, a potential "change-time" after which the physician prescribing preference has changed is estimated for each physician. Then, all patients of a given physician are divided into 2 homogeneous subsets: those treated before the change-time versus those treated after the change-time. The alternative IV is defined as the proportion of all previous patients in a corresponding homogeneous subset who were prescribed anti-VEGF.

Uncontrolled confounding from patient lifestyle factors, disease severity for comorbidities, and clinical treatment indications would give rise to biased effect estimates. Sensitivity analysis techniques are best used to assess the magnitude of these biases (Vanderweele & Arah, 2011). Beyond the suggested factors, there are likely other important covariates that are yet to be recognized in the association of AT events with anti-VEGF. No compensation can be made for such yet-to-be-discovered covariates.

One case control study in the investigation of the AT adverse event-anti-VEGF association is Campbell's study nested Case–Control study of patient exposure to the anti-VEGF drugs, Avastin and Lucentis, in the 180-day period before incident stroke and MI (Campbell, Gill, Bronskill, Paterson, Whitehead, & Bell, 2012). Their study population was similar to my study population with respect to age, gender, and recorded comorbidities. They found no statistically significant association between stroke and exposure to Avastin (adjusted OR 0.95; 95% CI, 0.68 to 1.34) or Lucentis (adjusted OR 0.87; 95% CI 0.68 to 1.10). They also found no significant association between acute MI and exposure to Avastin (adjusted OR 1.04; 95% CI 0.77 to 1.39) or Lucentis (adjusted OR 0.90; 95% CI 0.72 to 1.11). Their study included 1477 stroke cases, 2229 MI cases, and event-free controls matched 5:1. Cases were defined by admission to hospital with a primary diagnosis of ischemic stroke or acute MI, thus, the study did not capture any adverse events that did not lead to hospital admission or an emergency department visit. The number of exposed cases (ie, stroke cases and MI cases who received anti-VEGF) was considerably small, with only 138 stroke cases and 214 MI cases. The source population consisted of patients diagnosed as having any retinal disease and not AMD specifically. Additionally, patients were enrolled in the study over a five-year period and there was no consideration for the element of time. These factors likely attenuated Campbell's estimated measures of effect.

The magnitude and direction of my observed odds ratio of 1.186 is very similar to what Thulliez, et al reported for major cardiovascular events associated with anti-VEGF therapy in a meta-analysis of 21 randomized control trials (OR 1.18;95% CI, 0.81-1.71) (Thulliez, et al., 2014). However, the statistic from Thulliez's meta-analysis is less stable than what was obtained in my study as their confidence interval was wide and it included the null. The width of Thulliez's confidence interval may be attributable to the rare occurrence of major cardiovascular events

associated with anti-VEGF therapy in their meta-analysis sample size of 9557 patients, compared to the 153,000 person size of my study.

The results of my logistic regression adjusting for a history of AT events and weighted for propensity scores, separately in participants who did, and who did not receive anti-VEGF (model five) was reflective of a selection bias likely due to physicians electing to not give anti-VEGF to patients with a history of AT events. The results suggested that there were unmeasured variables beyond the baseline variables that were included in my propensity scores, informing physician treatment decisions and patient preferences. The bias was differential and may have influenced my estimates in either direction.

My study analyzed a population that is very similar to patients being treated in regular clinical practice by regular physicians. Participants were only excluded if they were not over age 50 years, if they did not have at least two recorded diagnoses of nvAMD (to minimize the probability of misclassification), if they were not enrolled in their health plan for 365 days prior to their first nvAMD diagnosis (to allow for assessment of confounding by comorbidities and concomitant medications), or if they were not newly-diagnosed (to avoid a survivor bias). No patient was excluded on the basis of clinical factors such as previous cardiovascular events.

My analysis underlined the importance of considering patient-time on study and confounding by indication. The switch from an odds ratio of 0.77 to 1.18 when these factors were considered showed their measurement is essential to developing point estimates of anti-VEGF-related AT adverse event risks that can be used to inform future treatment decision analysis and guideline recommendations for patients with AMD.

CHAPTER FIVE

Manuscript 3: "A Study of Arterial Thromboembolic Event Risk with Individual Anti-Vascular Endothelial Growth Therapies – Avastin, Lucentis and Eylea."

ABSTRACT

The current accepted standard treatment for neovascular age-related macular degeneration (nvAMD) consists of intravitreal injections of anti-vascular endothelial growth factor including Avastin (bevacizumab), Lucentis (ranibizumab), and Eylea (aflibercept). The aim of this study was to examine arterial thromboembolic (AT) event risk by patient treatment subgroups for each of the three drugs. I used Cox proportional hazard models and propensity score weighting to account for different patient follow-up times, and to balance the differences between treated and untreated participants that may have contributed to treatment decisions.

My analysis of 153,019 nvAMD patients registered in the MarketScan® database of insurance claims between 2006-2012 revealed 77,005 (50.32%) did not receive any anti-VEGF therapy in the observation period. Overall, 42,077 (27%) received Avastin, 20,969 (13%) Lucentis, and 12,968 (8%) Eylea.

Non-fatal AT events were up to 20% (hazard ratio [HR] 0.80, 95% confidence interval [CI] 0.75, 0.85) less likely to occur within the first 30 days, and 10% (HR 0.90, 95% CI 0.87, 0.93) less likely within days 31- 60 of the post-injection period in patients who received anti-VEGF than those who did not. In addition, AT events were more likely to occur when follow-up was longer. Kaplan-Meier curves portrayed a switch from negative to null risk (HR 0.94, 95% CI 0.92, 0.97) after 90 days, suggesting no further effect of anti-VEGF after approximately 90 days.

There were also clinically and statistically significant differences among the medications. The adjusted HRs for Eylea were highest and reflected a ratio close to 1.0 at 30, 60 and 90 days. The HRs for Avastin were lowest, and suggested 25% decrease in risk at day 30, 12% decrease

at day 60, and 11% decreased risk at day 90.

The apparent protective effect of Avastin and Lucentis that I observed in the first 90 days after nvAMD diagnosis could be ascribed to increased vigilance for, and early treatment of symptoms predictive of AT events in the anti-VEGF-treated patients during that phase.

INTRODUCTION

Arterial thromboembolic (AT) events are potentially fatal events associated with intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy in the treatment of neovascular age-related macular degeneration (nvAMD) (Costagliola, et al., 2012). Arterial thromboembolic events are thought to arise from VEGF suppression, since VEGF functions in many of the physiological and pathological processes that govern the development of AT adverse events (Carneiro, Falcao, Barthelmes, & et al., 2012). Several different anti-VEGF agents are used in nvAMD treatment, and there may be differences in the suppression of physiologic vascular endothelial growth factor (VEGF) activity associated with VAV therapy from different drugs.

Much of the basis for expecting differences in AT event rates among anti-VEGF therapies rests on laboratory evidence. Avery, et al evaluated plasma-free VEGF after first and third injections of intravitreal Lucentis, Avastin, and Eylea in a total of 56 nvAMD patients (Avery, et al., 2014). In the Eylea group, the mean plasma VEGF levels dropped below the lower limit of quantitation (LLOQ) as early as 3 hours postdose and remained below LLOQ until 7 days or more postdose. Plasma values for Avastin showed large suppression of free VEGF as well, although somewhat less than Eylea. Suppression due to Avastin was greatest after the third injection, presumably as a result of systemic accumulation of Avastin. In contrast, the mean free (unbound) VEGF levels following Lucentis injections showed minimal change. Yoshida, et al similarly demonstrated a significant decrease in plasma VEGF levels after administration of Eylea (Yoshida, 2014). The mean (SD) plasma VEGF levels were 280.0 (170.3) pg/ml before the

intravitreal injection and 8.2 (12.9) pg/mL after 1 day, 9.1 (9.1) pg/mL after 1 week, and 41.9 (41.4) pg/mL after 1 month ($p < 0.0001$, versus before injection). Again, there was no significant reduction in the mean plasma VEGF levels in the Lucentis group, being 245.7 (233.4) pg/mL before the injection, 246.6 (304.8) pg/mL after 1 day, 217.8 (212.9) pg/mL after 1 week, and 260.0 (290.1) pg/mL after 1 month.

Zehetner, et al measured serum VEGF levels using ELISA following anti-VEGF therapy, and showed that while Avastin significantly reduced the level of VEGF in the blood plasma for up to one month in patients with nvAMD, no significant systemic effects resulting from intravitreal Lucentis activity on plasma VEGF could be observed (Zehetner, 2013). The mean (SD) plasma VEGF concentration before injection of Avastin was 89.7(106.4) pg/mL. Concentration was reduced to 25.1(10.5) pg/mL after 7days ($p=0.01$), and to 22.8 (12.4) pg/mL even after 1 month ($p=0.008$). In contrast, the VEGF levels in patients treated with Lucentis did not change statistically significantly from baseline.

Park reported that intravitreally injected Avastin enters the systemic circulation and affects systemic VEGF levels (Park, et al., 2014). On the contrary, Lucentis cannot be found in the systemic circulation and does not affect systemic VEGF levels. The observed systemic level in an Avastin group, with anti-VEGF concentrations before the injection, after 1 day, 1 week, 1month being 110.1 ng/mL, 169.1 ng/mL, 215.6 ng/mL, and 152.5 ng/mL, respectively ($p=0.003$, 0.001, 0.004, versus baseline for each of the time points). Vascular endothelial growth factor systemic concentrations rose and fell gradually over 30 days but did not return to the initial concentration. The systemic VEGF concentrations were 102.7 pg/mL, 54.8 pg/mL, 25.1 pg/mL, and 37.0 pg/mL, before injection, after 1 day, and 1 week, and 1month respectively ($p=0.101$, 0.005, 0.007 versus baseline for each of the time points). In the Lucentis group, anti-VEGF concentrations before the injection, after 1 day, and 1 week, and 1 month were 200.7 ng/mL, 149.3 ng/mL, 132.7 ng/mL, and 155.4 ng/mL, respectively ($p=0.086$, 0.008, 0.066,

versus baseline for each of the time points) and VEGF concentrations were 48.0 pg/mL, 43.6 pg/mL, 85.9 pg/mL, and 73.3 pg/mL, respectively (p=0.285, 0.214, 0.263, versus baseline for each time point respectively).

Avery reported that all three agents rapidly moved into the bloodstream, but Lucentis very quickly cleared, whereas Avastin and Eylea demonstrated systemic exposure over a longer time period, and produced a marked reduction in plasma-free VEGF (Avery, et al., 2014). They observed that following a first dose, systemic exposure to Eylea was 5-, 37-, and 9-fold higher than Lucentis, whereas, Avastin was 9-, 310-, and 35-fold higher than Lucentis, based on geometric mean ratio of peak and trough concentrations and area under the curve, respectively. A third dose showed accumulation of Avastin and Eylea but not Lucentis. Eylea substantially suppressed plasma-free VEGF, with mean levels below the LLOQ (10 pg/mL) as early as 3 hours postdose until ≥7 days postdose. Mean free (unbound) VEGF levels with Lucentis were largely unchanged, with a mean trough level of 14.4 pg/mL compared to17 pg/mL at baseline.

In aggregate, these studies indicate that VEGF suppression appears greatest with Eylea and least with Lucentis. They suggest that the risk of AT events should be highest with Eylea and least with Lucentis use. My study looked for differences in the independent effects of the three drugs on anti-VEGF mediated AT event rates. I examined this clinically relevant issue that has a bearing on practice patterns, from a database that is sufficiently powered to explore rate differences in low-rate adverse events such as AT events, and reflects a real-world setting unlike the regulatory settings in which the issue has been previously explored.

SPECIFIC AIM AND HYPOTHESIS

To examine the independent effect of Avastin, Lucentis, and Eylea on the risk of potentially fatal AT events following anti-VEGF therapy for AMD in regular clinical practice.

Null hypothesis: There are no differences in AT event rates considering type of anti-VEGF injections.

STATISTICAL ANALYSIS

I classified study participants by the injection they received most frequently (ie, Avastin, Lucentis or Eylea). If there was an even frequency, I randomized them solely to one medication group or the other. However, this simple classification process may have biased my effect measure towards the null, due to some obviation of the differences between the anti-VEGF medication groups. I compared participants in the three medication subgroups for differences in their age, gender, insurance plan types, number of comorbidities, number of injections received, and other covariates using chi-square tests.

I performed Cox proportional hazard regression for all of the drugs in combination and then by medication subgroup, with the outcome variable AT event as the status variable and "time-to-first-event" as the time variable. All my analyses included inverse probability of treatment weighting (IPTW) based on the propensity score model described in the Appendix II. My potential predictors (ie, covariates) were age at nvAMD diagnosis, gender, number of days spent in hospital in 365-day period prior to nvAMD diagnosis, number of hospital visits, number of medication prescriptions filled in the 90-day period prior to nvAMD diagnosis, insurance plan type, most common concomitant medications, history of AT event, history of allergic drug reaction, history of non-allergic drug reaction, history of comorbidities (ie, diabetes mellitus, hypertension, hypercholesterolemia, myocardial infarction, congestive heart failure, atrial fibrillation, cerebrovascular accident, dementia, cancer, chronic obstructive pulmonary disease, peripheral vascular disease, renal disease), and total number of injections.

I tested four models. Model 1 was an unadjusted model, model 2 was adjusted for propensity score weights, model 3 adjusted for propensity score weights and all of the potential predictors,

model 4, which was the final model, adjusted for propensity score weights and variables selected by a backward stepwise selection process. Results were presented as hazard ratios (HR) and 95% confidence interval (CI). Statistical significance was defined as $P < 0.05$.

RESULTS

I considered nvAMD patients continuously enrolled in insurance subscriptions recorded in the MarketScan® dataset between 2006-2012 as a nvAMD study cohort (Figure 5-1). Study participants ranged in age from 50 to 108 years (median 80 years), and females comprised 60% of the study group.

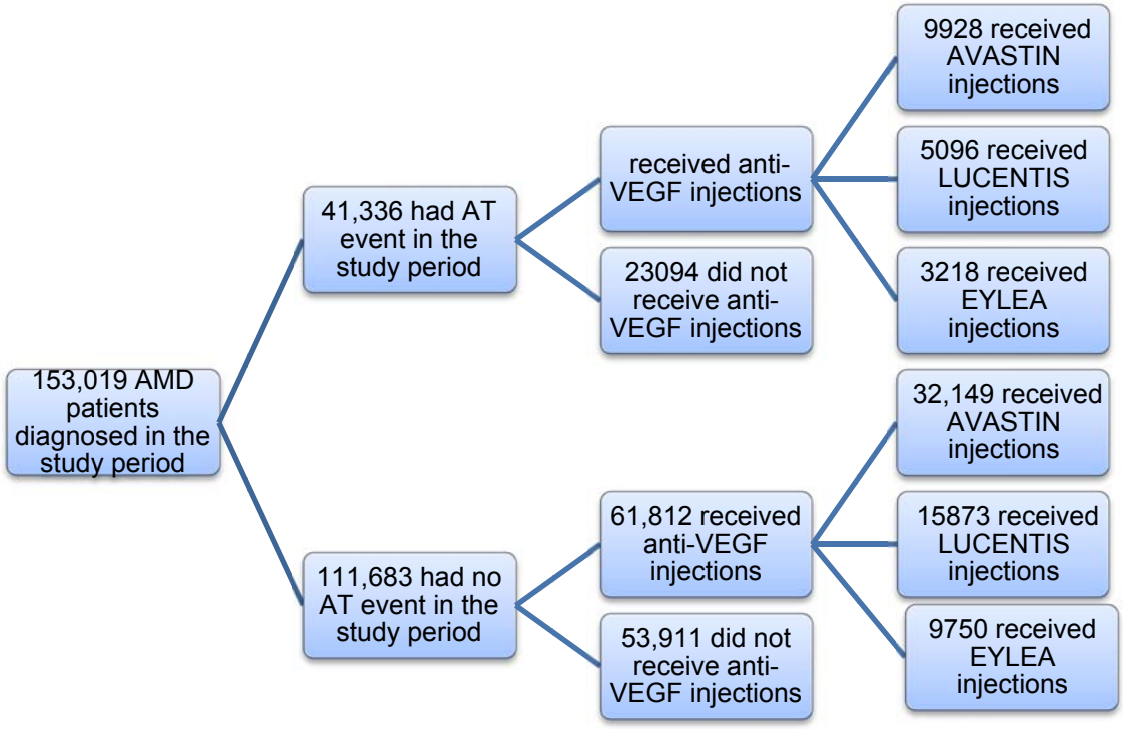

Figure 5-1. Consort diagram showing therapeutic sub-groups.

Of the 153,019 participants, 76,014 (49.7%) received anti-VEGF therapy during the observation period (Table 5-1). I found that 27% received Avastin, 13% Lucentis, and 8% Eylea, after partitioning patients to the anti-VEGF they received most frequently. Claims records for 41,336 (27% of the overall sample) participants showed AT events after their diagnosis of nvAMD. Of these, 15% did not have anti-VEGF therapy, 6.5% had Avastin, 3.3% had Lucentis and 2.1% had Eylea (Table 5-2).

Table 5-1. Injections received by participants

Group	Frequency	Percentage
None	77,005	50.32
Avastin	33,062	21.60
Lucentis	16,055	10.46
Eylea	9,563	6.23
Other[a]	17,334	11.39
TOTAL	153,019	100

[a]Patients who switched from one anti-VEGF to the other; these patients were randomized to the anti-VEGF treatment they received most.

Table 5–2. Injections received by participants grouped by AT event outcome

ATEventEver*	Avastin	Lucentis	Eylea	n	Percent
0	0	0	0	53911	35.23
0	1	0	0	32149	21.01
0	0	1	0	15873	10.37
0	0	0	1	9750	6.37
1	0	0	0	23094	15.09
1	1	0	0	9928	6.49
1	0	1	0	5096	3.33
1	0	0	1	3218	2.1
TOTAL				153,019	100%

*Note: 0 = no AT event after nvAMD diagnosis, 1 = had AT event after nvAMD diagnosis

My comparison of participants who received the three different anti-VEGF therapies (Table 5-3) showed that participants who received Avastin were younger than those who received Lucentis or Eylea (mean age for Avastin 79.0 years, 81.0 years for Lucentis and Eylea, p<0.0001). Across all anti-VEGF therapy groups, female participants were predominantly represented. When considering the ten most frequent comorbidities, there were no statistically significant differences in the number of patient comorbidities by anti-VEGF therapy group. A higher frequency of participants receiving Eylea or Lucentis had Medicare comprehensive insurance, whereas most participants receiving Avastin had PPO or Health Management Organization type subscriptions (Figure 5-2).

Table 5–3. Comparison of participants who received different injections

	Avastin	Eylea	Lucentis
Age, mean (95% CI)[a]	79.0 (70.0, 85.0)	81.0 (75.0, 86.0)	81.0 (75.0, 86.0)
Sex (n, %)[b]			
Male	8496 (40.17)	8829 (38.34)	5381 (37.12)
Female	12,653 (59.83)	14201 (61.66)	9115 (62.18)
Number of comorbidities, mean (95% CI)[c]	1.00 (0.00, 3.00)	1.00 (0.00, 3.00)	1.00 (0.00, 3.00)

[a]Kruskal-Wallis chi-square=662.85, df=2, p<0.0001
[b]Chi-square=35.84, df=2, p=1.65e-08
[c]Kruskal-Wallis chi-square=166.43, df=2, p<0.0001

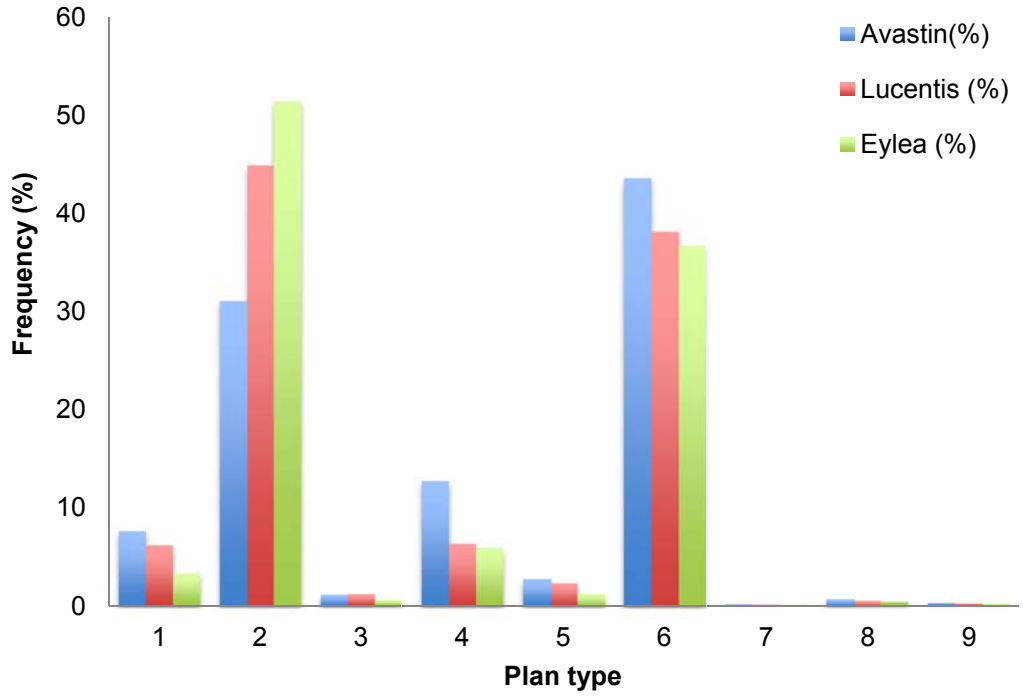

Figure 5–2. Insurance Plan Type for Participants by Medication

Note: Chi-square test, Chi-square = 2503.34, df = 16, p-value = <0.0001
1 – Basic Medicare, 2 – Comprehensive Medicare, 3- Exclusive provider organization, 4- Health management organization, 5- Point of service (POS) 6 – Preferred provider organization, 7 – POS with capitation, 8- Consumer-directed health plan, 9- High-deductible health plan

In IPTW weighted Cox proportional hazard models for 30, 60, and 90 days following the first recorded nvAMD diagnosis (Table 5-4), AT events were up to 20% (HR 0.80, 95% CI 0.75, 0.85) less likely to occur within the first 30 days, and 10% (HR 0.90, 95% CI 0.87, 0.93) less likely within the first 60 days for patients who received anti-VEGF than those who did not. At 90 days, AT events were 6% less likely to occur and by 365 days the AT event risk was null. Kaplan-Meier curves for any anti-VEGF therapy crossed from negative to null risk (HR 0.94, 95% CI 0.92, 0.97) after 90 days (Figure 5-3).

Table 5-4. Hazard ratios for AT event outcomes for any anti-VEGF therapy

Predictor for AT events	HR	LL	UL
VEGF, 30 days	0.80	0.75	0.85
VEGF, 60 days	0.90	0.87	0.93
VEGF, 90 days	0.94	0.92	0.97
VEGF, 365 days	1.0	0.98	1.02

AT=arterial thromboembolic, LL=lower limit, HR=hazard ratio, UL=upper limit, VEGF=vascular endothelial growth factor

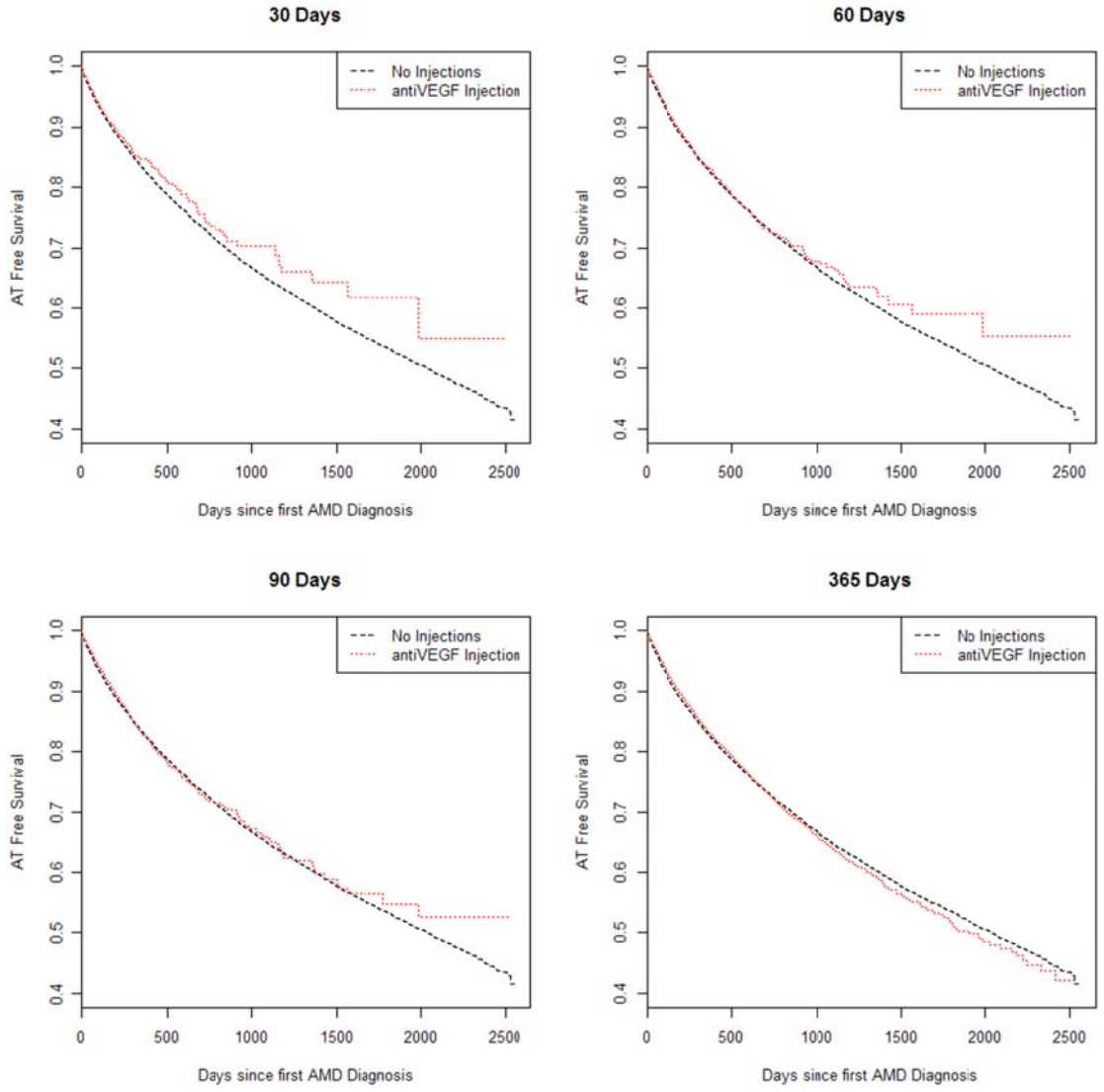

Figure 5-3. Kaplan-Meier curves showing survival after 30, 60 and 90 days for patients with and without anti-VEGF injections

When I stratified by anti-VEGF therapy group (Table 5-5), the adjusted hazard ratios for Avastin therapy showed a 25% lower AT event risk at day 30 than for participants who did not receive anti-VEGF therapy. Arterial thromboembolic event risk with Lucentis was also 18% lower, but

there was no difference in risk for the Eylea group (HR 0.99, 95% CI 0.85,1.15) compared with participants who were not on treatment. At day 60, Avastin and Lucentis showed similarly lower (12% and 11% respectively) AT event risk, while there was no change in the null risk shown with Eylea. At day 90, AT event risk for the Avastin group remained 12% lower, but there was null risk for the group under Lucentis therapy compared with participants who were not on treatment.

Table 5-5. Hazard ratios for AT events, stratifying by anti-VEGF therapy group

AT Event Outcomes	Avastin HR (LL, UL)	Lucentis HR (LL, UL)	Eylea HR (LL, UL)
30 Days	0.75 (0.69,0.81)	0.82 (0.73,0.92)	0.99 (0.85,1.15)
60 Days	0.88 (0.84,0.92)	0.89 (0.84,0.96)	0.99 (0.90,1.08)
90 Days	0.89 (0.86,0.92)	1.10 (1.01,1.15)	0.89 (0.83,0.95)
365 Days	1.03 (1.01,1.05)	0.98 (0.96,1.01)	0.92 (0.89,0.94)

AT=arterial thromboembolic, HR=hazard ratio, LL=lower limit, UL=upper limit

DISCUSSION

My study results suggested that AT events are up to 20% less likely to occur within the first 30 days after nvAMD diagnosis in patients who receive anti-VEGF therapy, and more likely to occur when follow-up is longer. The results demonstrated an apparent protective effect of any anti-VEGF therapy against AT adverse events for up to 90 days, in comparison with participants who did not receive therapy. I consider that the early decrease in risk may be due to increased physician vigilance and early treatment of clinical signs and symptoms that are predictive of AT events.

The reduction in risk in the early time period after injections in my study is comparable to the observation by Curtis, et al when considered alongside a similar study in the same population that Curtis investigated (Curtis, Hammill, Schulman, & Cousins, 2010). In Curtis' study, they

observed a 1-year cumulative incidence of MI ranging from 1.1 to 1.3 cases per 100, and 1-year cumulative incidence of stroke, ranging from 1.8 to 2.1 cases per 100, in an anti-VEGF-treated cohort of Medicare nvAMD patients. These incidence rates were lower than those reported by Alexander, et al. among untreated Medicare, new-onset nvAMD patients, where 2.2 per 100 nvAMD patients were hospitalized for MI during 1 year of follow-up and 3.5 per 100 patients were hospitalized for hemorrhagic or ischemic stroke (Alexander, Linde-Zwirble, Werther, Depperschmidt, Wilson, & Palanki, 2007). Curtis reported an association of MI with anti-VEGF, but contrary to my results, they reported no statistically significant relationship between anti-VEGF therapy and stroke. However, in participant selection, only patients with a primary history of stroke were included, thus patients who whose diagnosis of stroke was second or third on the claims form were excluded from their analysis.

In a study of the Australian department of Veteran Affairs administrative claims database, Pratt, et al also reported no elevated risk of ischemic stroke in the first 30 days post-Lucentis anti-VEGF initiation (Pratt, 2014). They reported an incidence rate ratio [IRR] of 1.36 (95 % CI 0.98–1.88). Pratt noted that elevated risk was observed for those who received therapy for 31–60 days (IRR 1.91; 95 % CI 1.13–3.24). Contrary to my results and Curtis' study, Pratt et al reported no association for MI in either time period (1–30 days, IRR 0.90, 95 % CI 0.65–1.23; 31–60 days, IRR 0.98, 95 % CI 0.54–1.79). However, the study considered only hospitalized patients, and did not include outpatient MI diagnoses.

When stratified by medication type, my study showed an apparent protective effect of Avastin and Lucentis against AT adverse events in treated participants compared to untreated participants that gradually reduced towards the null over a 90-day period. Eylea did not demonstrate such a protective effect, and evidenced null risk at the 30,60 and 90 day points. The difference I observed between Eylea and the other two drugs suggests that even with increased physician vigilance in the early treatment period, AT adverse events may occur with

Eylea. However, the number of patients in the Eylea group was smallest, and the Eylea sub-group had been on the study for the shortest amount of time therefore the results must be interpreted with caution.

Contrary to my results, an analysis by Wang, et al concluded that the risks of ischemic stroke and MI do not differ significantly between Avastin and Lucentis injections (Wang X. , 2014). Kemp, et al also observed no statistically significant difference in incidence of stroke rates in their 12-month study of AT events after injections of Avastin or Lucentis compared to photodynamic therapy and a nontreated community sample (Kemp, et al., 2013). Their study included 1267 participants treated with anti-VEGF, 399 participants treated with photodynamic therapy, and 1763 community controls, all aged 50 years or above. Kemp, et al did however observe a higher 12-month MI rate for any anti-VEGF-treated participants than photodynamic therapy participants or the community group (1.9/100 vs. 0.8 and 0.7, respectively). The adjusted MI rate in anti-VEGF-treated participants was 2.3 times greater than the community group (95% CI, 1.2–4.5) and photodynamic therapy participants (95% CI, 0.7–7.7). No dose-response was observed, as the 12-month MI risk did not increase with the number of injections administered (HR, 0.9; 95% CI, 0.5–1.5). Although Kemp's study adjusted for comorbidities, the community cohort was described as having a greater prior stroke risk than the treated sample, and the extent of residual confounding was therefore unknown. Neither Wang nor Kemp's investigations included Eylea.

There are certain limitations of my study. Diagnosis entries in the MarketScan® database could not be verified and misclassification may have occurred. Such misclassification is unlikely to have affected treated and untreated study participants differentially, and non-differential misclassification would bias my estimates of effect toward the null.

Since Avastin is used off-label, it is possible that nvAMD was recorded as the indication for treatment for Eylea and Lucentis which are FDA-approved, compared to Avastin. This information bias would affect my estimates that are stratified by anti-VEGF therapy and drive the estimated differences among the three therapies away from the null.

Lucentis and Eylea are much more expensive than Avastin, and cost-considerations affect physician and patient treatment considerations. Although I had no information on the socio-economic status of participants, I compared the characteristics of the treated populations for each of the drugs and adjusted my effect estimates for confounding accordingly.

Some patients first received one type of injection, then were switched to another if there was no response. This implies that there may be differences among patients who received the combinations of the injections, and participants were assigned by the drugs they received most frequently. Additionally, the use of the different drugs changed perceptibly over the study period. Avastin has been in use since 2005, Lucentis was introduced to the market in 2006, and Eylea in 2011. Patients may also have been switched around in a nonrandom fashion as newer agents were introduced. I selected my simple method of assignment in the face of all the complexities that surround choice of anti-VEGF therapy, and may have biased my effect estimates towards the null by reducing the differences between patient treatment groups.

In conclusion, none of the anti-VEGF therapies appreciably increased the risk of an AT event above that expected for a matched, untreated population, suggesting that all three drugs are equally acceptable with respect to their risk-benefit ratio. If the drugs altered the likelihood of developing nvAMD in the untreated eye through their infiltration of the systemic circulation, that might have been an additional appropriate benefit consideration; however, such an analysis is outside the scope of this study.

CHAPTER SIX

Overall Conclusions and Future Directions

The results from my analysis of insurance claims for 153,019 neovascular age-related macular degeneration (nvAMD) study participants identified from the MarketScan® database between January 2006 and December 2012, showed differences in risk for adverse arterial thromboembolic (AT) events that were plausibly related to decreased VEGF levels following anti-VEGF. The effects were complex and not uniform across all time periods.

In my first study, I investigated risk factors for AT adverse events in anti-VEGF-treated patients and found a 3-fold adverse event risk in patient that have a history of AT events prior to anti-VEGF treatment. I also found that treatment with the medication, Plavix, was associated with a 60% increase in risk. Additionally, diagnoses of cerebrovascular or peripheral arterial disease produced approximately 40% increased AT adverse event risk, while adult-onset diabetes was associated with about 30% increased risk. Careful monitoring would be advisable for nvAMD patients with a history of AT event, or on treatment with Plavix, or diagnosed with cerebrovascular disease, peripheral arterial disease or adult-onset diabetes if anti-VEGF therapy is prescribed.

In my second study, I examined the odds for AT events associated with any anti-VEGF therapy, and found the adjusted odds of AT adverse event 20% lower (odds ratio [OR] 0.796, 95% confidence interval [CI] 0.777, 0.816) under anti-VEGF treatment than without treatment. However, when I included patient time in the study, and propensity score weights in the logistic regression, the apparent protective effect reversed to almost 20% increased odds (OR 1.185, 95% CI 1.168, 1.203) of AT events in patients on anti-VEGF. The change in direction and magnitude of effect suggested a time-varying effect of anti-VEGF in association with AT events.

In my third study I performed Cox regression with propensity score IPTW for any anti-VEGF,

and for the three anti-VEGF types – Avastin, Lucentis and Eylea, individually. I found that AT events are up to 20% (hazard ratio [HR] 0.80, 95% CI 0.75, 0.85) less likely to occur within the first 30 days, and 10% (HR 0.90, 95% CI 0.87, 0.93) less likely within the first 60 days of the post-injection period in patients who receive any anti-VEGF than those who do not. My Kaplan-Meier curves showed that AT events were more likely to occur when follow-up was longer, and demonstrated a change from negative to null risk after 90 days, with a suggestion of no further effect of anti-VEGF after approximately 90 days.

In the individual drug analyses, I found that Avastin and Lucentis lowered AT event risk in the first 90 days after nvAMD diagnosis for study participants who received, than for those did not receive anti-VEGF therapy. However, there was no difference in AT adverse event risk over the same time period between those study participants who did, or did not receive Eylea.

I applied both Cox and logistic regression models in my studies. The Cox regression and logistic regression are very different analyses, most notably in how they treat time. In my logistic model I did adjust for time, but time was assumed to have a quadratic effect; whereas in the Cox regression, the time component was non-parametric and the parameters corresponded to a proportional shift in the (non-linear and-non parametric) hazard function estimated. The Cox models had a much more flexible effect of time than could be allowed in logistic regression and this lead to a better definitive analysis.

Overall, the results of my study indicate that no anti-VEGF therapy significantly increases AT event risk. However, a person with a prior history of AT event has such a markedly increased risk with anti-VEGF therapy, that greater surveillance or mitigation of other risk factors would be appropriate.

APPENDICES

List of Figures, List of Tables, List of Symbols, List of Acronyms, Supplementary Materials, Glossary

Note: For ease of reference especially for non-clinical readers, the non-proprietary anti-VEGF names Avastin, Lucentis and Eylea have been used instead of the generic names Bevacizumab, Ranibizumab and Aflibercept respectively.

Appendix I. ICD-9 Codes for Comorbidities

Comorbidities	ICD-9 CODES
Cerebrovascular disease	430-438
Chronic obstructive pulmonary disease	490-496
Coronary heart disease	402, 411, 413
Dementia	294.1
Atrial fibrillation	427.31
Coronary artery bypass graft	36.11-36.16
Cancer in previous 5 years	140-239
Chronic renal insufficiency	585.1-585.9
Diabetes	250-250.93
Hypertension	401-405
Peripheral arterial dx	443.9
obesity	278
hypercholesterolemia	272.0-272.4

Appendix II. Propensity Score Model

Family: binomial
Link function: logit
Parametric coefficients:

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	0.01692	0.02001	0.845	0.397912
PLANTYP2	0.19881	0.02065	9.626	< 2e-16 ***
PLANTYP4	0.02365	0.02515	0.940	0.347073
PLANTYP6	0.18091	0.01996	9.065	< 2e-16 ***
Norvasc	0.28862	0.04643	6.217	5.07e-10 ***
Plavix	-0.05269	0.02953	-1.784	0.074345 .
Lipitor	0.07696	0.02839	2.711	0.006707 **
Crestor	0.22302	0.05047	4.419	9.93e-06 ***
Tricor	0.12566	0.05207	2.413	0.015809 *
Toprol	0.22501	0.04172	5.394	6.90e-08 ***
Xalatan	0.06096	0.04108	1.484	0.137900
AtHx	0.18042	0.12518	1.441	0.149492
StrokeHx	-0.42695	0.12380	-3.449	0.000563 ***
MIHx	-0.29124	0.10827	-2.690	0.007147 **
AllerReact	-0.01705	0.04266	-0.400	0.689329
NonAllerReact	-0.03268	0.04476	-0.730	0.465238
CVD	-0.07566	0.07311	-1.035	0.300737
COPD	-0.03097	0.01636	-1.892	0.058445 .
CHD	-0.09928	0.02473	-4.015	5.95e-05 ***
Dementia	-0.51431	0.08287	-6.206	5.44e-10 ***
AtrialFib	-0.09705	0.01919	-5.057	4.25e-07 ***
CABG	-0.26867	0.06849	-3.923	8.75e-05 ***
Cancer	-0.02979	0.01324	-2.250	0.024453 *
Renal	-0.14463	0.02715	-5.327	9.98e-08 ***
Diabetes	-0.11129	0.01484	-7.499	6.45e-14 ***
Hypertension	-0.06323	0.01237	-5.113	3.18e-07 ***
PeriArt	-0.11523	0.02832	-4.069	4.73e-05 ***
Obesity	-0.10710	0.04643	-2.307	0.021073 *
Cholesterolemia	-0.12786	0.01293	-9.890	< 2e-16 ***
EyeAuto	-0.22735	0.03542	-6.418	1.38e-10 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Approximate significance of non-linear terms:

	edf	Ref.df	Chi.sq	p-value
s(mSVCDATEy)	18.572	18.974	1155.118	< 2e-16 ***
s(AgeDx)	7.734	9.568	760.758	< 2e-16 ***
s(TotalMeds90)	14.090	16.010	6951.662	< 2e-16 ***

```
s(HospDays)     1.004  1.008    2.194     0.14
s(NVisits)      3.659  3.931   31.343 2.68e-06 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

R-sq.(adj) =  0.0925   Deviance explained = 7.42%

n = 153019

KEY
Insurance plan type
PLANTYP2 Comprehensive medicare
PLANTYP4 Health management organization
PLANTYP6 Preferred provider organization

Medication prescription filled in 365 days before AMD diagnosis
Norvasc
Plavix
Lipitor
Crestor
Tricor
Toprol
Xalatan

Comorbidity recorded in 365 days prior to AMD diagnosis
AtHx
StrokeHx   History of stroke
MIHx       History of MI
AllerReact  History of allergic drug reaction
NonAllerReact  History of non-drug allergic reaction
CVD            Cardiovascular disease
COPD           Chronic obstructive pulmonary disease
CHD            Chronic heart disease
Dementia       Dementia
AtrialFib      Atrial fibrillation
CABG           History of CABG procedure
Cancer         History of cancer
Renal          History of renal disease
Diabetes       Diabetes
Hypertension    Hypertension
PeriArt        Peripheral arterial disease
Obesity        Obesity
Hypercholesterolemia  Hypercholesterolemia
EyeAuto        Autoimmune eye disease
```

Appendix III. Full Results of Cox Regression for Each Model

MODEL ONE: Unadjusted Cox proportional hazards model

	Coef.	SE	P	HR	LL	UL
VEGF	0.0088	0.0115	0.4431	1.01	0.986	1.03

MODEL TWO: After adjustment for propensity score weights (IPTW)

	Coef.	SE	P	HR	LL	UL
VEGF	0.0362	0.00685	1.269e-07	1.04	1.02	1.05

MODEL THREE: After adding baseline covariates to the model

	Coef.	SE	P	HR	LL	UL
VEGF	0.148	0.00745	<0.0001	1.16	1.14	1.18
AgeDx	0.154	0.00506	<0.0001	1.17	1.15	1.18
I(AgeDx^2)	-0.000773	3.26e-05	<0.0001	0.999	0.999	0.999
HospDays	-0.000147	0.000924	0.8735066	1	0.998	1
NVisits	0.00138	0.000398	0.0005132	1	1	1
I(NVisits^2)	-6.6e-07	3.19e-06	0.8360590	1	1	1
TotalMeds90	-0.000954	6.95e-05	<0.0001	0.999	0.999	0.999
PLANTYP2	-0.0583	0.0122	1.670e-06	0.943	0.921	0.966
PLANTYP4	0.00306	0.0167	0.8549837	1	0.971	1.04
PLANTYP6	0.0247	0.0122	0.0437182	1.02	1	1.05
Norvasc	-0.0827	0.031	0.0075479	0.921	0.866	0.978
Plavix	0.4	0.0152	<0.0001	1.49	1.45	1.54
Lipitor	-0.0308	0.0176	0.0792903	0.97	0.937	1
Crestor	-0.085	0.0351	0.0152817	0.918	0.857	0.984
Tricor	0.0277	0.0326	0.3960302	1.03	0.964	1.1
Toprol	0.0419	0.0252	0.0965075	1.04	0.993	1.1
Xalatan	-0.0556	0.0255	0.0290468	0.946	0.9	0.994
AtHx	1.13	0.00938	<0.0001	3.08	3.03	3.14
AllerReact	-0.00168	0.0256	0.9478176	0.998	0.949	1.05
NonAllerReact	-0.0144	0.0278	0.6052011	0.986	0.933	1.04
CVD	0.314	0.0338	<0.0001	1.37	1.28	1.46
COPD	0.0911	0.00975	<0.0001	1.1	1.07	1.12
CHD	0.156	0.0135	<0.0001	1.17	1.14	1.2
Dementia	0.0815	0.0421	0.0528223	1.08	0.999	1.18
AtrialFib	0.148	0.0107	<0.0001	1.16	1.14	1.18
CABG	-0.00582	0.0496	0.9065160	0.994	0.902	1.1
Cancer	-0.0315	0.00827	0.0001393	0.969	0.953	0.985
Renal	0.222	0.0152	<0.0001	1.25	1.21	1.29
Diabetes	0.198	0.00884	<0.0001	1.22	1.2	1.24
Hypertension	0.0439	0.00767	1.033e-08	1.04	1.03	1.06
PeriArt	0.344	0.0144	<0.0001	1.41	1.37	1.45
Obesity	0.0213	0.0322	0.5071200	1.02	0.959	1.09
Hypercholesterolemia	0.0733	0.00805	<0.0001	1.08	1.06	1.09

MODEL FOUR: Testing for effect measure modification by including interaction terms in the model and testing for their significance

	Coef.	SE	P	HR	LL	UL
VEGFever	-1.07	0.404	0.0078502	0.342	0.155	0.754
AgeDx	0.155	0.00655	<0.0001	1.17	1.15	1.18
I(AgeDx^2)	-0.000792	4.23e-05	<0.0001	0.999	0.999	0.999
HospDays	0.001	0.00104	0.3356782	1	0.999	1
NVisits	0.00422	0.000533	2.442e-15	1	1	1.01
I(NVisits^2)	-1.25e-05	4.29e-06	0.0035413	1	1	1
TotalMeds90	-0.0181	0.000386	<0.0001	0.982	0.981	0.983
PLANTYP2	-0.0733	0.0189	0.0001011	0.929	0.896	0.964
PLANTYP4	-0.00467	0.0231	0.8399610	0.995	0.951	1.04
PLANTYP6	-0.0161	0.019	0.3976019	0.984	0.948	1.02
Norvasc	-0.0927	0.0433	0.0324378	0.911	0.837	0.992
Plavix	0.483	0.019	<0.0001	1.62	1.56	1.68
Lipitor	-0.0098	0.0232	0.6730819	0.99	0.946	1.04
Crestor	-0.0507	0.0471	0.2815787	0.951	0.867	1.04
Tricor	0.0503	0.0442	0.2545933	1.05	0.964	1.15
Toprol	0.0105	0.0347	0.7622825	1.01	0.944	1.08
Xalatan	0.0898	0.0325	0.0056894	1.09	1.03	1.17
AtHx	1.18	0.0122	<0.0001	3.27	3.19	3.35
AllerReact	-0.0443	0.0332	0.1819254	0.957	0.896	1.02
NonAllerReact	0.024	0.0356	0.4997229	1.02	0.955	1.1
CVD	0.339	0.0404	<0.0001	1.4	1.3	1.52
COPD	0.0824	0.0134	7.225e-10	1.09	1.06	1.11
CHD	0.131	0.0171	1.776e-14	1.14	1.1	1.18
Dementia	0.0285	0.0466	0.5407996	1.03	0.939	1.13
AtrialFib	0.144	0.0145	<0.0001	1.15	1.12	1.19
CABG	0.073	0.0586	0.2131138	1.08	0.959	1.21
Cancer	-0.025	0.0113	0.0269837	0.975	0.954	0.997
Renal	0.155	0.0197	2.998e-15	1.17	1.12	1.21
Diabetes	0.23	0.012	<0.0001	1.26	1.23	1.29
Hypertension	0.111	0.011	<0.0001	1.12	1.09	1.14
PeriArt	0.326	0.0183	<0.0001	1.39	1.34	1.44
Obesity	0.0462	0.0416	0.2665295	1.05	0.965	1.14
hypercholesterolemia	0.114	0.011	<0.0001	1.12	1.1	1.15
VEGF:AgeDx	0.0264	0.0105	0.0116526	1.03	1.01	1.05
VEGF:I(AgeDx^2)	-0.000149	6.71e-05	0.0262593	1	1	1
VEGF:HospDays	-0.00661	0.00225	0.0032772	0.993	0.989	0.998
VEGF:NVisits	-0.00556	0.000825	1.603e-11	0.994	0.993	0.996
VEGF:I(NVisits^2)	2.43e-05	6.92e-06	0.0004443	1	1	1
VEGF:TotalMeds90	0.018	0.000393	<0.0001	1.02	1.02	1.02

VEGF:PLANTYP2	0.0336	0.0247	0.1732471	1.03	0.985	1.09
VEGF:PLANTYP4	-0.0491	0.0344	0.1531043	0.952	0.89	1.02
VEGF:PLANTYP6	0.0739	0.0248	0.0029380	1.08	1.03	1.13
VEGF:Norvasc	0.0511	0.062	0.4092684	1.05	0.932	1.19
VEGF:Plavix	-0.143	0.032	7.847e-06	0.867	0.814	0.923
VEGF:Lipitor	0.0231	0.0355	0.5152745	1.02	0.955	1.1
VEGF:Crestor	-0.0245	0.0706	0.7279881	0.976	0.85	1.12
VEGF:Tricor	0.015	0.0655	0.8184770	1.02	0.893	1.15
VEGF:Toprol	0.0977	0.0505	0.0528241	1.1	0.999	1.22
VEGF:Xalatan	-0.27	0.0524	2.673e-07	0.764	0.689	0.846
VEGF:AtHx	-0.189	0.0193	<0.0001	0.828	0.797	0.86
VEGF:AllerReact	0.067	0.0524	0.2007996	1.07	0.965	1.18
VEGF:NonAllerReact	-0.149	0.0573	0.0092586	0.862	0.77	0.964
VEGF:CVD	-0.131	0.0743	0.0785904	0.877	0.759	1.02
VEGF:COPD	0.0443	0.0196	0.0234953	1.05	1.01	1.09
VEGF:CHD	0.0334	0.0279	0.2314051	1.03	0.979	1.09
VEGF:Dementia	-0.119	0.111	0.2838057	0.888	0.715	1.1
VEGF:AtrialFib	0.0172	0.0216	0.4265657	1.02	0.975	1.06
VEGF:CABG	-0.406	0.11	0.0002321	0.667	0.537	0.827
VEGF:Cancer	-0.0132	0.0166	0.4271489	0.987	0.955	1.02
VEGF:Renal	0.144	0.031	3.466e-06	1.15	1.09	1.23
VEGF:Diabetes	-0.0417	0.0178	0.0190923	0.959	0.926	0.993
VEGF:Hypertension	-0.11	0.0155	1.229e-12	0.896	0.869	0.923
VEGF:PeriArt	0.0131	0.0296	0.6592281	1.01	0.956	1.07
VEGF:Obesity	-0.0875	0.0657	0.1827361	0.916	0.806	1.04
VEGF:hypercholesterolemia	-0.0965	0.0162	2.731e-09	0.908	0.88	0.937

MODEL FIVE: Final model

Predictor	Coef.	SE	P	HR	LL	UL
Toprol	0.0558	0.0224	0.0127667	1.06	1.01	1.1
NonAllerReact	-0.0395	0.025	0.1137851	0.961	0.915	1.01
CHD	0.145	0.0121	< .00001	1.16	1.13	1.18
Cancer	-0.0322	0.00742	1.401e-05	0.968	0.954	0.982
PeriArt	0.331	0.0128	< .00001	1.39	1.36	1.43
EyeAuto	0.0585	0.0194	0.0025630	1.06	1.02	1.1
VEGF	-1.22	0.361	0.0007681	0.296	0.146	0.602
AgeDx	0.153	0.00583	< .00001	1.17	1.15	1.18
I(AgeDx^2)	-0.000775	3.77e-05	< .00001	0.999	0.999	0.999
HospDays	-1.28e-05	0.000835	0.9877795	1	0.998	1
NVisits	0.00511	0.000488	< .00001	1.01	1	1.01
I(NVisits^2)	-2.28e-05	4.21e-06	< .00001	1	1	1
TotalMeds90	-0.0183	0.000346	< .00001	0.982	0.981	0.983
PLANTYP2	-0.0849	0.0168	< .00001	0.919	0.889	0.949
PLANTYP4	-0.0266	0.0207	0.1981363	0.974	0.935	1.01
PLANTYP6	-0.0239	0.0169	0.1585356	0.976	0.945	1.01
Plavix	0.465	0.0169	< .00001	1.59	1.54	1.65
Xalatan	0.045	0.0293	0.1254252	1.05	0.988	1.11
AtHx	1.19	0.0108	< .00001	3.28	3.21	3.35
CVD	0.352	0.0361	< .00001	1.42	1.32	1.53
COPD	0.0625	0.012	< .00001	1.06	1.04	1.09
AtrialFib	0.135	0.0129	< .00001	1.14	1.12	1.17
CABG	0.00759	0.053	0.8862437	1.01	0.908	1.12
Renal	0.156	0.0175	< .00001	1.17	1.13	1.21
Diabetes	0.239	0.0107	< .00001	1.27	1.24	1.3
Hypertension	0.105	0.00979	< .00001	1.11	1.09	1.13
Cholesterolemia	0.0942	0.00979	< .00001	1.1	1.08	1.12
VEGF:AgeDx	0.0291	0.00934	0.0018352	1.03	1.01	1.05
VEGF:I(AgeDx^2)	-0.000165	5.99e-05	0.0057541	1	1	1
VEGF:HospDays	-0.00462	0.00194	0.0169548	0.995	0.992	0.999
VEGF:NVisits	-0.00736	0.000708	< .00001	0.993	0.991	0.994
VEGF:I(NVisits^2)	4.22e-05	6.18e-06	< .00001	1	1	1
VEGF:TotalMeds90	0.0183	0.000352	< .00001	1.02	1.02	1.02
VEGF:PLANTYP2	0.0532	0.022	0.0153944	1.05	1.01	1.1
VEGF:PLANTYP4	-0.0344	0.0308	0.2642867	0.966	0.91	1.03
VEGF:PLANTYP6	0.0628	0.0222	0.0045909	1.06	1.02	1.11

VEGF:Plavix	-0.114	0.0284	5.620e-05	0.892	0.844	0.943
VEGF:Xalatan	-0.182	0.0467	9.349e-05	0.833	0.76	0.913
VEGF:AtHx	-0.182	0.0172	< .00001	0.833	0.806	0.862
VEGF:CVD	-0.171	0.0651	0.0087909	0.843	0.742	0.958
VEGF:COPD	0.0722	0.0174	3.466e-05	1.07	1.04	1.11
VEGF:AtrialFib	0.037	0.0192	0.0545227	1.04	0.999	1.08
VEGF:CABG	-0.338	0.0974	0.0005304	0.713	0.589	0.864
VEGF:Renal	0.122	0.0275	< .00001	1.13	1.07	1.19
VEGF:Diabetes	-0.0492	0.0158	0.0019114	0.952	0.923	0.982
VEGF:Hypertension	-0.0992	0.0137	< .00001	0.906	0.882	0.93
VEGF:Cholesterolemia	-0.0698	0.0144	< .00001	0.933	0.907	0.959

Appendix IV. Full Results of Logistic Regression for Each Model

MODEL ONE: Unadjusted odds ratio

	OR	LL	UL	p
(Intercept)	0.4284	0.4218	0.435	< .00001
VEGFEver	0.7371	0.7206	0.754	< .00001

MODEL TWO: Adjusted odds ratio

	OR	LL	UL	p
(Intercept)	0.019	0.01711	0.0211	0.0001
VEGFEver	0.7963	0.7771	0.8159	<0.0001
AgeDx	1.038	1.036	1.039	<0.0001
SEX2	0.8499	0.8294	0.871	<0.0001
HospDays	0.9945	0.991	0.9981	0.0029019
NVisits	1.004	1.003	1.005	<0.0001
TotalMeds90	1.003	1.003	1.004	<0.0001
Hx of AT event	3.605	3.475	3.739	<0.0001
CVD	1.455	1.258	1.684	4.386e-07
COPD	1.064	1.027	1.101	0.0004917
CHD	1.285	1.222	1.352	<0.0001
Dementia	0.6566	0.5561	0.7752	6.925e-07
AtrialFib	1.043	1.003	1.085	0.0358861
CABG	0.8688	0.7373	1.024	0.0929878
Cancer	0.9447	0.9179	0.9723	0.0001080
Renal	0.9954	0.941	1.053	0.8722846
Diabetes	1.263	1.224	1.303	<0.0001
Hypertension	0.9836	0.9577	1.01	0.2239685
PeriArt	1.354	1.279	1.432	<0.0001
Obesity	0.6706	0.5983	0.7517	6.677e-12
Cholesterolemia	0.8498	0.8261	0.8743	<0.0001

MODEL THREE: Adjusted odds ratio after adding patient time as a covariate

	OR	LL	UL	p
(Intercept)	2.979	2.892	3.068	< .00001
VEGFEver	1.086	1.07	1.102	< .00001
StudyDuration	0.3051	0.2988	0.3116	< .00001
I(StudyDuration^2)	1.113	1.109	1.116	< .00001

MODEL FOUR: Adjusted odds ratio after adding IPTW, patient time and AT event history as covariates

	OR	LL	UL	p
(Intercept)	1.988	1.927	2.051	< .00001
VEGFEver	1.185	1.168	1.203	< .00001
StudyDuration	0.3499	0.3424	0.3575	< .00001
I(StudyDuration^2)	1.096	1.093	1.099	< .00001
History of AT event	3.198	3.128	3.269	< .00001

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